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# ABSTRACT

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Ambika Maria: Emotional speech and affective touch processing in children less than 2 years of age.
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Speech and touch are fundamental ways of communicating emotions in infancy and early childhood. However, little is known about emotional processing in children. The aim of this dissertation was to examine emotional speech and affective touch processing in children less than two years of age. **Study I** was a systematic review on emotional processing studies done using near-infrared spectroscopy in children up to two years of age. **Study II** examined two-month-old infant brain responses to different types of emotional speech using diffuse optical tomography (DOT); and **Study III** explored their association with self-reported maternal pregnancy-related anxiety. **Study IV** investigated affective touch processing in two-year-old children by using DOT.

Bilateral temporal cortical activation was most commonly reported in response to emotional stimuli in children less than two years of age in earlier studies using NIRS (**Study I**). In two-month-old infants, we found a positive HbT response to happy > neutral speech in the left posterior superior temporal sulcus (pSTS) and happy > angry speech in the left superior temporal gyrus (STG) and pSTS (**Study II**). We found that infant HbT responses to sad speech, over left STG and mid-insula, correlated negatively with pregnancy-related anxiety symptoms at gestational week 24 (**Study III**). We observed a positive HbT response to affective touch in the left inferior frontal gyrus (IFG) and left middle temporal gyrus in two-year-old children (**Study IV**).

Our results demonstrate that two-months-old infants show differential activation to happy speech as compared to neutral and angry speech. In addition, two-month-old infants' attenuated processing of sad speech associates with maternal prenatal pregnancy-related anxiety during mid-pregnancy. Lastly, affective touch is processed in two-year-old children in the key components of the "social brain", and thus affective touch probably plays an important role in forming social bonds between children and their caregivers.

Keywords: brain, emotion, speech, touch, children, infants, maternal stress, maternal anxiety, maternal distress, near-infrared spectroscopy (NIRS), diffuse optical tomography (DOT).

# TIIVISTELMÄ

Turun yliopisto, Lääketieteellinen tiedekunta, Psykiatria, Turun kliininen tutkijakoulu, FinnBrain-syntymäkohorttitutkimus, Turku, Suomi
Ambika Maria: Emotionaalisen puheen ja affektiivisen kosketuksen käsittely alle kaksivuotiaiden lasten aivoissa.
Väitöskirja, Annales universitatis turkuensis, Serial D 1421,
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Puhe ja kosketus ovat keskeisiä tapoja viestiä tunteita lapsuudessa. Hyvin vähän kuitenkin tiedetään tunteiden prosessoinnista lasten aivoissa. Tämän väitöskirjan tarkoituksena oli tutkia tunneäänien ja tunnepitoisen kosketuksen prosessointia alle 2 vuotiailla lapsilla. **Tutkimus I** oli systemaattinen katsaus tunteiden prosessoinnista 0-2 vuotiailla lapsilla käyttäen lähi-infrapunaspektroskopiaa. **Tutkimus II** selvitti kahden kuukauden ikäisten vauvojen aivovasteita eri tyyppisille tunneäänille käyttäen diffuusia optista tomografiaa (DOT); ja **Tutkimus III** keskittyi selvittämään näiden aivovasteiden yhteyttä raskauteen liittyvään ahdistuneisuuteen, jota mitattiin PRAQ-R2 kyselylomakkeella raskauden aikana. **Tutkimus IVssä** tutkittiin kaksivuotiaiden lasten tunnepitoisen kosketuksen aivovasteita DOTia käyttäen. Havaitsimme, että temporaalilohkon aktivaatio lapsilla aivojen kummallakin puolella oli tavallisin vaste tunnestimuluksille kun tutkimusmenetelmänä käytettiin NIRSiä alle 2 vuotiailla lapsilla (**Tutkimus I**). Kahden kuukauden ikäisillä vauvoilla havaitsimme positiivisen HbT-vasteen iloiselle > neutraalille puheäänelle vasemman puolen posteriorisessa superiorisessa temporaalisulkuksessa (pSTS) ja iloiselle > vihaiselle puheäänelle vasemman puolen superiorisessa temporaaligyruksessa (STG) (**Tutkimus II**). Havaitsimme myös, että vauvojen HbT vasteet surulliselle puheäänelle vasemman puolen STGssa ja insulan keskiosassa korreloivat negatiivisesti raskauteen liittyviin ahdistuneisuusoireisiin raskausviikolla 24 (**Tutkimus III**). Osoitimme lisäksi, että tunnepitoinen kosketus aiheuttaa positiivisen HbT vasteen vasemman puolen inferiorisessa frontaaligyruksessa (IFG) ja vasemman puolen temporaalilohkon keskiosassa kaksivuotiailla lapsilla (**Tutkimus IV**).Tuloksemme osoittavat, että kahden kuukauden ikäisten vauvojen aivot reagoivat eri tavalla iloiseen puheääneen kuin neutraaliin ja vihaiseen puheääneen. Lisäksi tämän ikäisten vauvojen korostuneet vasteet surulliselle puheäänelle liittyivät äidin raskauteen liittyvään ahdistuneisuuteen. Lopuksi kävi ilmi, että tunnepitoista kosketusta prosessoidaan kaksivuotiaiden lasten aivoissa keskeisillä “sosiaalisten aivojen” alueilla ja siksi tunnepitoisella kosketuksella todennäköisesti on merkittävä rooli sosiaalisten siteiden muodostamisessa lasten ja heitä hoitavien aikuisten välillä.

Avainsanat: aivot, tunne, puhe, kosketus, lapset, vauvat, äidin stressi, äidin ahdistuneisuus, lähi-infrapunaspektroskopia (NIRS), diffuusi optinen tomografia (DOT).

## TABLE OF CONTENTS

# ABBREVIATIONS

NIRS – Near-infrared Spectroscopy

fNIRS – Functional NIRS

fMRI – Functional Magnetic Resonance Imaging

DOT- Diffuse Optical Tomography

(HD-) DOT- (High density) Diffuse Optical Tomography

CT – C-tactile

C-LTMR – C low-threshold mechanoreceptor

FOV – Field of View

HbO2 – Oxygenated Hemoglobin

HbR – Deoxygenated Hemoglobin

HbT – Total Hemoglobin

ROI – Region of Interest

S1 – Primary Somatosensory Cortex

S2 – Secondary Somatosensory Cortex

PRAQ-R2 – Pregnancy Related Anxiety Questionnaire Revised-2

gwk – gestational week

ANOVA – Analysis of variance

# LIST OF ORIGINAL PUBLICATIONS

I Maria, A., Shekhar, S., Nissilä, I., Kotilahti, K., Huotilainen, M., Karlsson, L., Karlsson, H. & Tuulari, J. J. (2018) Emotional Processing in the First 2 Years of Life: A Review of Near-Infrared Spectroscopy Studies. Journal of neuroimaging: official journal of the American Society of Neuroimaging, 28(5), 441-454.

II Shekhar, S.[*], Maria, A.[*], Kotilahti, K., Huotilainen, M., Heiskala, J., Tuulari, J. J., Hirvi, P., Mustaniemi, H., Hiltunen, P., Karlsson, L., Karlsson, H. & Nissilä, I. (2019). Hemodynamic responses to emotional speech in two-month-old infants imaged using diffuse optical tomography. Scientific Reports, 9(1). doi:10.1038/s41598-019-39993-7. http://creativecommons.org/licenses/by/4.0/
[*]Equal contribution.

III Maria, A., Shekhar, S., Nissilä I., Kotilahti, K., Tuulari, J. J., Hirvi, P., Huotilainen, M., Heiskala, J., Karlsson, L. & Karlsson, H. (2019). Maternal Pregnancy-related Anxiety is associated with Infant Brain Responses to Emotional Speech. (manuscript)

IV Maria, A., Kotilahti, K., Hirvi, P., Heiskala, J., Tuulari, J. J., Karlsson, L., Karlsson, H. & Nissilä, I. (2018). Inferior frontal gyrus and middle temporal cortical activation in response to affective touch in two-year-old children. (manuscript)

The thesis is based on the above original publications, which are referred to in the text as Studies I – IV. The original publications have been reproduced with the permission of the copyright holders.

# 1 INTRODUCTION

Speech is the most common way of communication in humans (Scherer, 1986). Although, it is extensively researched in adults and children; surprisingly, there are limited amount of studies on how different types of emotional speech are processed in infants. Further, it is unclear whether infant brain responses to emotional speech are related to the psychological distress experienced by their mothers during pregnancy. Maternal psychological distress, including symptoms of trait anxiety, pregnancy-specific anxiety and depression has been linked with adverse offspring outcomes postnatally (Schetter and Tanner, 2012; Van den Bergh et al., 2005a; Otte et al., 2015; Van den Huevel et al., 2015; Van den Bergh et al., 2017). Nevertheless, no reported study has revealed associations between maternal pregnancy-specific anxiety and infants' processing of different types of emotional speech.

In early childhood, touch is an integral part of parent-infant interactions (Jean et al., 2009) and is critical for the emotional and cognitive development of infants (Hertenstein & Campos, 2001; Stack, 2001; Hertenstein, 2002; Mcglone and Reilly, 2010). Interpersonal touch is the earliest form of human communication (Frank, 1957) and is an important non-verbal way of communicating emotions (Barnett, 1972; Hertenstein et al., 2009). Touch in social interactions promotes liking of a person or place, trust, compliance and cooperation among individuals (Fisher et al., 1976; Crusco and Wetzel, 1984; Hornik, 1992; Burgoon et al., 1992; Kleinke, 1997; Joule and Guéguen, 2007; Morrison 2010). However, there are scanty to none reported studies about affective touch processing in toddlers.

In this thesis, emotional processing in children less than two years of age was explored by a systematic review of studies using near-infrared spectroscopy (NIRS) (Study I), the cortical processing of emotional speech in two-month-old infants was examined (Study II) and a potential connection between maternal prenatal pregnancy-related anxiety and infant neural hemodynamic responses to speech was explored (Study III). Moreover, the cortical processing of affective touch in two-year-old children was investigated (Study IV).

This thesis contributes to the knowledge on emotional speech processing in infants. Importantly, it demonstrates, that maternal pregnancy-specific anxiety during mid-pregnancy might affect infant brain's hemodynamic responses to the emotional speech. Even more, this thesis fills an important gap in the literature on affective touch processing in two-year-old children.

# 2 REVIEW OF LITERATURE

## 2.1 Emotions: definition and role

Emotions can be defined as the outcomes of the process of assessing the world in terms of one's own concerns which lead to changes in readiness to execute action, or changes in attentional arousal, or tendencies to establish, maintain, or disrupt relationships within the environment (Frijda, 1986). According to Izard (1977), there are three essential components of emotion: "(a) the experience or conscious feeling of emotion, (b) the processes that occur in the brain and nervous system, and (c) the observable expressive patterns of emotion, particularly those on the face" (Izard, 1977). "Basic emotions" are the emotions that have been classified in terms of changes in the readiness to execute action (Frijda, 1986). These basic emotions were traditionally classified into happiness, surprise, anger, fear, sadness, and disgust (Ekman and Friesen, 1975). Adding to these emotions, distress, interest, contempt, guilt and shame were added as basic emotions by Izard in 1977 (Izard, 1977). A newer socio-dynamic model of emotions states that emotions are dynamic entities that emerge from social interactions and relationships; and that emotions are functional to specific socio-cultural context in which they emerge (Mesquita and Boiger, 2014).

Emotions play a fundamental role in motivating and focusing individuals and are instrumental in social communication (Izard, 2010). In interpersonal interactions, we make use of emotions to understand the intentions of others and to convey our own intentions. Emotional cues are of particular importance in parent-child interactions as the children pick up on them to navigate their way in the social life. Emotions can be conveyed through facial expressions, voice, speech, touch, gestures and body language. Out of these, speech and touch (gentle caressing by the caregiver) are one of the primary modes of communication in parent-child interactions.

## 2.2 Neuroimaging in investigating emotion processing

Over the last three decades, there has been an increasing interest in unravelling the neural basis of emotion. In the 1900s, with the advent of magnetic resonance imaging (MRI), it was easier to identify brain lesions in adults with disorders in emotion processing. Using MRI, important brain structures associated with emotion processing were identified such as amygdala, medial prefrontal cortex, insula and somatosensory cortex (Mcdonald, 2017). Besides structural MRI, func-

tional magnetic resonance imaging (fMRI) and positron emission tomography (PET) have proved as important tools to localize brain activity in adults in response to emotional stimuli. Furthermore, functional near-infrared spectroscopy (fNIRS), which is a non-invasive technique to measure changes in hemoglobin concentration associated with the neuronal activity (Hoshi and Tamura, 1993; Jobsis, 1977; Schroeter et al., 2002), is increasingly used to investigate emotion in infants and children (Lloyd-Fox et al., 2010; Doi et al., 2013). Table 1 summarizes the different functional neuroimaging modalities used in investigating emotion processing in children.

**Table I: Comparison of different functional neuroimaging modalities used in investigating emotion processing in children. NIRS: Near-infrared Spectroscopy, EEG: Electroencephalography, fMRI: Functional Magnetic Resonance Imaging, MEG: Magnetoencephalography, $HbO_2$: Oxygenated Hemoglobin, HbR: Deoxygenated Hemoglobin, HbT: Total Hemoglobin and BOLD signal: Blood Oxygen-Level Dependent signal.**

| | **NIRS** | **EEG** | **fMRI** | **MEG** |
|---|---|---|---|---|
| Underlying principle | Changes in blood oxygenation based on hemodynamic changes, as reflected by $HbO_2$, HbT and HbR | Electromagnetic activations in the cortical parts of the brain<br><br>Postsynaptic potentials | Changes in deoxygenated hemoglobin content of the blood, BOLD signal | Electromagnetic activity resulting from activations in the cortical regions<br><br>Postsynaptic potentials |
| Long distance interactions | Able to analyze activations and deactivations (changes in HbT) | Able to analyze synchronous brain activity | Able to analyze changes associated with cerebral blood flow | Able to analyze synchronous brain activity |
| Cost | Moderate | Low | Expensive | Expensive |
| Mobility of Instrument | Mobile | Mobile | Immobile | Immobile |
| Noise | Silent | Silent | Noisy | Silent |

| | | | | |
|---|---|---|---|---|
| Restriction of movement | No | No | Yes, but little movement can be handled with software | No, but little to none movement is preferred to get good data. |
| Sensitivity to movement | Moderate | Moderate | High | High |
| Use with magnetic implants | Yes | Yes | No | No |
| Temporal resolution | ~100 Milliseconds | Milliseconds | 1-5 seconds | Milliseconds |
| Mother can hold the baby | Yes | Yes | No | No |
| Spatial resolution | Centimeters | Centimeters | Millimeters | Millimeters |
| Interference from hair | Yes | Some | No | No |
| Radial/ depth source detection | Limited depth penetration around 3 cm, Children > adults | Somewhat limited depth penetration, Children > adults | Yes | Limited depth penetration |
| Source localization limitation | Variable with optical properties of head tissues | Variable with electric properties of head tissues | Not dependent on tissue properties | Not dependent on tissue properties |

### *2.2.1 Diffuse optical tomography as a neuroimaging modality*

Diffuse Optical tomography (DOT) is used as a neuroimaging tool that is based on the underlying principles of NIRS. DOT uses multi-channel near-infrared (NIR) light, which diffusely illuminates the brain tissue (instead of following a straight path) with large source-detector separations on the surface of the tissue (Kotilahti, 2015). DOT is based on the principle that a limited set of measure-

ments of transmitted light between pairs of points on an object's surface can enable us to reconstruct a three-dimensional volume representing internal scatters and absorbers (Hebden et al., 2002). By measuring the transmitted light at large source-detector separations, the deeper tissues of the brain can be imaged (Jönsson, 2017; Jönsson et al., 2018). Subsequently, light integration over several seconds (or longer) per source reflects long-term oxygenation changes (and not fast hemodynamic or metabolic changes) in the underlying brain tissue (Hebden et al., 2002).

NIRS is an imaging method that uses near-infrared spectrum of light (650 to 1000 nm) to measure the tissue hemodynamics and oxidative metabolism (Ferrari et al., 2004; Quaresima et al., 2012; Torricelli et al., 2014). Functional NIRS (fNIRS) is the technique of using NIRS as a neuroimaging modality to assess brain activation in adults and children. In fNIRS, when near-infrared light is shone into the head, the light penetrates the scalp, skull and the underlying brain, where it is either scattered or absorbed by colored compounds called chromophores. The absorption occurs by chromophores of variable concentration (oxygen-dependent), such as hemoglobin (Hb) and cytochrome oxidase (terminal enzyme of respiratory chain), and by chromophores of fixed concentration (melanin). Furthermore, as seen in Fig. 1, the difference in the absorption spectra of the oxygenated hemoglobin (HbO2) and the deoxygenated hemoglobin (HbR), help us in separate quantification of HbO2 and HbR, as well as, the sum of these two compounds which is called the total hemoglobin (HbT). As 70-80 % of the blood in the brain is in the venous compartment, the predominant information we get from fNIRS is thought to be from the venous blood (Quaresima et al., 2012). Thus, the ratio of fNIRS signal from arterial to capillary to venous compartments is thought to be approximately 10:20:70 (Quaresima et al., 2012). For excellent work on the physical principles and utilities of NIRS please see Delpy and Cope, 1997; Rolfe, 2000; Strangman et al., 2002; Hoshi, 2003; Minagawa-Kawai et al., 2008; Wolf & Greisen, 2009; Lloyd-Fox et al., 2010; Gervain et al., 2011; Quaresima et al., 2012 and Torricelli et al., 2014.

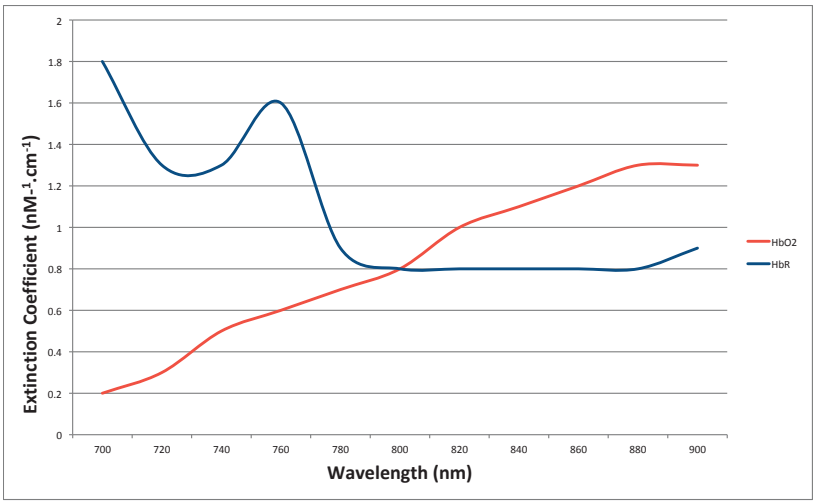


**Figure 1. Differential absorption spectra of oxygenated hemoglobin (HbO2) and deoxygenated hemoglobin (HbR) in the near-infrared spectral range (adapted from Zhao et al., 2017 and Cope, 1991).**

As far as the sensitivity of NIRS is concerned, the precise volume of brain that can be imaged by NIRS is dependent on the equipment parameters. Nevertheless, it is regarded that approximately for a source-detector separation of 3 cm, the maximum sensitivity will be found between the source and detector fiber tip location, and roughly 1.5 cm below the surface of the skin with a banana-shaped region of sensitivity extending both above and below this depth, e.g. Fig. 2 (Strangman et al., 2002; Ferrari et al., 2004).

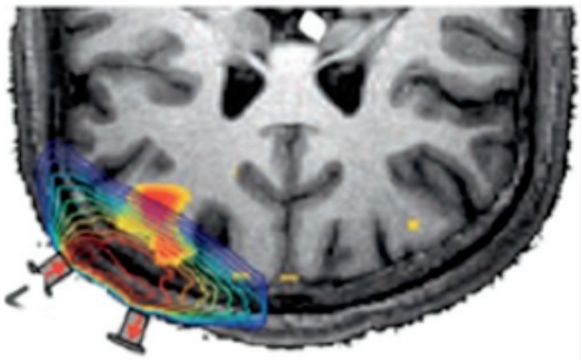

**Figure 2: Schematic diagram of the principle of near-infrared spectroscopy. Diagram created by Dr. Theodore Huppert; displayed by the permission of the creator.**

### *2.2.2 Emotion processing models*

In the 2000s, two models of emotion processing emerged. The first model was implicit and explicit processing, according to which emotional and social stimuli are processed initially by a subcortical pathway, comprising of amygdalae, insula, ventral striatum, anterior cingulate and prefrontal cortex and this process is fast, automatic and largely occurs outside conscious awareness of an individual (Lieberman, 2007; Phillips et al., 2003). Whereas, effortful processing of emotional stimuli is slow, deliberate, engages the cognitive processes and is mediated by a cortical pathway composed of the dorsal lateral and medial prefrontal cortex and anterior cingulate gyrus as well as hippocampus and temporo-parietal regions (Lieberman, 2007; Phillips et al., 2003; Mcdonald, 2017). The second model was that of a mirror system in recognizing others' emotions and empathizing with them. According to this model, when a person observes emotions, actions or tactile sensations in others, the same brain areas get activated in the observer, if he were to perform similar movements or experience similar emotions (Bastiaansen et al., 2009). This emotion simulation has been seen to primarily activate premotor, posterior parietal and somatosensory cortex of the observer (Bastiaansen et al., 2009).

Subsequently, there was a rise in studies investigating the role of emotion processing in the social behavior; leading to the development of a construct of social cognition that refers to the ability to understand the minds of others in relation to ourselves (Amodio & Frith, 2006). Social cognition is now broadly divided into cognitive theory of mind, which refers to understanding what the other person might think and believe, and affective theory of mind, which refers to understanding what the other person might feel (Mitchell & Phillips, 2015; Mcdonald,

2017). More recently, the role of cortex in emotion processing is being emphasized as it has been proposed that subcortical regions (like amygdala and pulvinar) assign the biological significance to an affective stimulus by coordinating the function of cortical networks (Pessoa & Adolphs, 2010). Therefore, it is useful to think in terms of neuronal connections between cortical and subcortical regions of the brain, rather than specific brain regions.

Thus, speech and touch (gentle caressing by the caregiver) are particularly important in investigating emotion processing as they are the primary ways of communicating emotions in parent-child interactions.

## 2.3 Emotional Speech

### *2.3.1 Speech as a means to convey emotion*

Speech is regarded as an especially effective means of conveying emotions, not only by the use of words but also, the way the words are spoken (Scherer, 1986). These emotional messages carried through speech are fundamental means of social communication in humans, likely important for evolutionary reasons, such as social cohesion and better survival (Darwin, 1872; Scherer, 1986, 1995; Bachorowski, 1999). For instance, fearful speech conveys threat-related information and, enables the listener to act promptly and get away from the impending danger (Darwin, 1872). The ability to decode basic emotions from vocal expression seems to develop already in infancy (Juslin & Laukka, 2003). Speech prosody refers to acoustic changes in speech that may occur by modulations of tempo and continuity, accentuation, pitch and range, timbre and dynamics of speech and vocalizations (Coutinho & Dibben, 2013). These emotion-specific prosodies help the speaker to convey the desired emotional meaning and enable the listener to understand the speaker's intended emotions (Frick, 1985; Juslin & Laukka, 2003; Coutinho & Dibben, 2013).

### *2.3.2 Speech perception*

Sound waves travel from the outer ear into the auditory canal and reach the inner hair cells of cochlea where the sound waves are converted into electric impulses. These electric impulses are then transported through the vestibulocochlear nerve, via the cochlear nuclei, the inferior colliculus and the medial geniculate body to the contralateral primary auditory cortex in the temporal lobe (Nieuwenhuys,

1984; Cope et al., 2015). The signal is then transported to the Wernicke's area on the left posterior superior temporal gyrus (STG) where speech comprehension takes place (Wernicke, 1874; Wernicke 1886/1977). Wernicke's area has been implicated in rapid interpretation and recognition of tight links in language whereas right temporal gyrus plays an important role in understanding coarser or broader meanings in language (Jung-Beeman, 2005, Harpaz et al., 2009). Giraud et al. (200) observed activation in Wernicke's area in response to acoustic complexity of the stimuli, auditory search and speech comprehension. In addition, dorsal part of Broca's area activation has been associated with attention; and bilateral insulae, anterior cingulate and right medial frontal cortex activation have been observed with the interaction of auditory attention and comprehension (Giraud et al., 2004). In infants, similar to that seen in adults, speech seems to activate left frontal and temporal cortical areas (Peña et al., 2003; Saito et al., 2009; Kotilahti et al., 2010; Naoi et al., 2012). Specifically, bilateral frontal, frontotemporal, temporal, and temporo-parietal regions have been implicated in speech processing in infants (Saito et al., 2007; Naoi et al., 2013). Although, a thorough discussion of the proposed models of speech information processing are beyond the scope of this thesis, they are described in studies by Zatorre et al., 1992 and Binder et al., 2000, and reviews by Hickok and Poeppel, 2000; Zatorre and Binder, 2000; Zatorre and Belin, 2001; Scott and Johnsrude, 2003 and Belin et al., 2004.

### *2.3.3 Perception of emotions from speech*

In adults, voice-selective brain regions are found in bilateral superior temporal sulcus (STS) (Belin, 2000), which process not only voice-specific information but also emotional prosody in voice (Grandjean et al., 2005; Ethofer et al., 2006). Besides STS, other brain areas implicated in processing emotional content of voice include inferior prefrontal cortex, orbitofrontal cortex, premotor cortical regions, amygdala, and insula (Fecteau et al., 2005; Warren et al., 2006; Fecteau et al., 2007; Morris et al., 1999; Sander and Scheich, 2001; Blasi et al., 2011).

Considering the importance of speech in social and emotional development of infants, an increasing number of neuroimaging studies have investigated emotional speech processing in infants. For instance, Zhang et al. (2017) reported that infants as early as 2-8 days of age seem to activate voice-selective areas on hearing emotional prosody (relative to neutral) in right temporal cortex (mainly the middle temporal gyrus and superior temporal gyrus), similar to that seen in adults (Zhang et al., 2017). Furthermore, a right parietal area (supramarginal gyrus) was noted to show a heightened sensitivity to fearful relative to happy and neutral

prosodies (Zhang et al., 2017). In contrast, left posterior temporal cortex, amygdala and orbitofrontal cortex are reportedly activated in 2-month-old infants in response to their mothers' voice (Dehaene-Lambertz et al., 2010). In infants (3-7-month-old), Blasi et al. observed right-lateralized voice-selective regions in the anterior STS and greater activation in orbitofrontal cortex and insula in response to sad voice as compared to neutral voice (Blasi et al., 2011). Grossmann et al., found that when 7-month-old infants listened to words spoken with neutral, happy, or angry prosody, emotional prosodies caused greater activation in right-lateralized voice-selective regions as compared to neutral prosody. Moreover, hearing angry prosody caused more activation in the right temporal cortex than the happy prosody. Furthermore, right inferior frontal gyrus showed particular sensitivity to happy prosody (Grossmann et al., 2010a), thereby suggesting the role of frontal cortex in the processing of happy voice.

Altogether, these studies indicate that already in infancy, emotions are differentially processed in the brain. However, one of the important questions that still remain unaddressed is the role of left hemisphere in emotional speech processing and how exactly the different emotions from speech are processed in infants.

## 2.4 Emotional processing in infants and maternal prenatal distress

Maternal prenatal distress has been associated with an increased susceptibility to behavioral and emotional problems in the offspring, later in life, such as schizophrenia, attention deficit hyperactivity disorder (ADHD), autism, and affective disorders (Goodman et al., 2011; Glover, 2014; Herba et al., 2016; Lahti et al., 2017; Martin et al., 1999; O'Connor et al., 2002; 2003; Udagawa and Hino, 2016; Van den Bergh and Marcoen, 2004; Van den Bergh et al., 2008, Van den Bergh et al., 2017; Van den Huevel et al., 2018; Wachs et al., 2009; Walder et al., 2014). Maternal prenatal generalized anxiety, pregnancy-specific anxiety or depression are related to specific neurodevelopmental changes in the offspring (Schetter and Tanner, 2012), such as impulsivity (Van den Bergh et al., 2005a), auditory attention (Harvinson et al., 2009; Hunter et al., 2012; Otte et al., 2015; Van den Huevel et al., 2015) and neuro-cognitive functioning (Davis & Sandman, 2010; Mennes et al., 2006, 2009; Van den Bergh et al., 2005a).

Although, extensive research indicates associations between maternal prenatal stress and increased risk of neurobehavioral problems in the children; the precise mechanism by which maternal prenatal stress affects the fetal neurodevelopmental pathways is still unclear. However, a few of the mechanisms proposed are that prenatal exposure to maternal stress leads to permanent alterations in fetal hypothalamic-pituitary-axis (Weinstock et al., 1992; Clarke et al., 1994; Henry et al.,

1994; Barbazanges et al., 1996; Maccari et al., 2003 & Grant et al., 2009), changes in functional and structural brain connectivity (Scheinost et al., 2017; Van den Bergh et al., 2017), changes in glucocorticoid receptor sensitivity, changes in proteins and neurotransmitters in the central nervous system (Matthews, 2000, 2002; Schwab et al., 2001; Wyrwoll and Holmes, 2012), changes in autonomic nervous system, cardiovascular system, immune system and gut microbiome (Bale et al., 2010; Bale, 2015; Griffiths and Hunter, 2014; Harris and Seckl, 2011; Meaney et al., 2007; Räikkönen et al., 2011; Seckl, 2004; Stroud et al., 2014, 2016; Van den Bergh et al., 2017). Moreover, it has also been observed that maternal psychological distress during pregnancy may lead to persistence of anxiety and depressive symptoms in the postnatal period (Dipietro et al., 2008), leading to lower quality of parental caregiving, which may lead to adverse effects on their child's neurodevelopment (Field et al., 2010).

Even though, maternal prenatal distress has been linked with altered neurodevelopmental outcomes in infants, it is not yet clear, which time period of gestation is the most sensitive period. Traditionally, several studies have suggested that the first half of the pregnancy is the most vulnerable period for altered neurodevelopmental outcomes (Mennes et al., 2009; Otte et al., 2015; Qui et al., 2015; Van den Bergh et al., 2005a; Van den Huevel et al., 2015). However, this view is now being challenged with the theory that there is not any specific vulnerable period of gestation and different mechanisms of prenatal stress effects may be operating at different points of gestation, affecting central nervous system, stress system and immune systems (Van den Bergh et al., 2005b, 2017). Nevertheless, further studies are needed to confirm this theory.

Recent studies have investigated links between maternal anxiety and altered cerebral processing in the prenatally exposed fetus (Qui et al., 2015). Maternal prenatal anxiety has been associated with changes in the auditory attention in the offspring (Harvinson et al., 2009; Hunter et al., 2012; Otte et al., 2015; Van den Huevel et al., 2015), as well as emotional problems in the children (Martin et al., 1999; O'Connor et al., 2002; 2003; Van den Bergh et al., 2004). However, to our knowledge, there are no reported studies on association between maternal pregnancy-related anxiety during gestation and emotional speech processing in infants.

## 2.5 Touch

### *2.5.1 Importance of touch in childhood*

Touch is one of the most developed sensory modality at birth and contributes to the brain development throughout infancy and childhood (Stack, 2001; Hertenstein, 2002; Mcglone and Reilly, 2010). Touch has been considered the ultimate signal that the caregiver is present and the infant is safe in stressful situations (Main, 1990). Importantly, touch is crucial for the socio-emotional, cognitive and physical development in infants (Field, 1988; Greenough, 1990; Hertenstein and Campos, 2001; Stack, 2001; Hertenstein, 2002). Maternal affectionate touch has been observed to decrease infants' physiological reactivity to stress and contribute to their neurobehavioral growth (Feldman & Eidelman, 2003, 2004; Feldman et al., 2010).

Touch plays a significant role in not only eliciting positive emotions (Peláez-Nogueras et al., 1997), but also, modulating negative emotional expressions in infants (Hertenstein and Campos, 2001). For instance, infants as early as 1.5- to 3.5-months of age, who received tactile stimulation from an adult, have been observed to make more eye contact, give more smiles and vocalizations, and spend less time crying and protesting, as compared to the infants who did not receive tactile stimulation (Peláez-Nogueras et al., 1996). Not only maternal, but also skin-to-skin contact between fathers and infants has been associated with improved respiration, oxygenation, glucose levels, and cortisol in neonates (Bauer et al., 1996; Christensson, 1996; Mörelius et al., 2015; Shorey et al., 2016). Furthermore, paternal touch has been related to less crying, better vocal interactions, and more relaxed behaviour in infants (Erlandsson et al., 2007; Velandia et al., 2010; Shorey et al., 2016). Similarly, five-month-old infants displayed significantly less grimacing and more smiling when their mothers touched them, as compared to infants whose mothers had not touched them (Stack and Muir, 1992).

The benefits of touch have been increasingly used in clinical settings for infants. For example, skin-to-skin contact between infants and primary caregiver has been proven beneficial for premature infants and is used commonly as "kangaroo-care" method in hospitals (Field and Chaitow, 2000). Skin-to-skin contact also has an analgesic effect on babies undergoing minor procedures such as heel-prick (Gray et al., 2000; Herrington and Chiodo, 2004). Thus, touch is a crucial component of the mutual emotional regulation between a child and a caretaker and is critical in how the child experiences others in his surroundings (Tronick, 1995).

### 2.5.2 Discriminative and affective touch

The somatosensory system comprises of peripheral afferent nerve fibers and specialized peripheral receptors that process information about proprioception from joints and muscles, and cutaneous senses (Mcglone and Reilly, 2010). Traditionally, cutaneous senses or sense of touch includes four sub-modalities of pressure/vibration, pain, temperature and itch (McGlone et. al., 2014). Touch stimuli at the skin surface is converted to electrical impulses that are carried to the central nervous system by set of neurons called low-threshold mechanoreceptors (LTMs) (Jenkins and Lumpkin, 2017). These LTMs are innervated by large, myelinated fibers called Aβ afferents (McGlone et. al., 2014; Kandel et al., 2013; Mountcastle, 2005) that enable rapid processing of sensory-discriminative dimensions of touch (Voos et al., 2013; Morrison et al., 2010).

Besides the sensory-discriminative dimension of touch, motivational-affective forms the second dimension of touch, also referred to as social or 'affective' touch (Morrison et al., 2010). The affective role of touch in humans is considered to be mediated by thin, unmyelinated, low-threshold mechanoreceptor units called C-tactile (CT) afferents (McGlone et. al., 2014; Olausson et al., 2010). C-fiber tactile afferents were first identified in saphenous nerve of cats by Zotterman in 1939 (Zotterman, 1939). In humans, CT afferents were first reported using microneurography recordings in the infraorbital nerve (Johansson et al., 1988) and supraorbital nerve (Nordin, 1990) from the face. Thereafter, these CT afferents were also found in the arms and the legs (Vallbo et al., 1993, 1999; Edin, 2001; Wessberg et al., 2003; Campero et al., 2011). Interestingly, CT afferents are exclusively seen in the hairy skin (e.g., forearm and leg) and appear to absent in the glabrous skin (e.g., palms) (Vallbo et al., 1999; Liu et al., 2007). CT afferents have been reported to be activated most effectively by soft brushing stroking at a speed of 3-10 cm/s over hairy skin and this speed of stroking has been perceived as most pleasant by adults (Vallbo et al., 1993; Löken,et al., 2009). Besides CT-fibers, Aβ fibers may also play a role in the affective touch processing, as similar touch to the palm (where CT fibers are absent) can also be perceived as pleasant (Krämer et al., 2007).

### 2.5.3 Affective touch processing

Animal studies have reported that CT afferents characteristically project to lamina I/II of the dorsal horn of the spinal cord (Light et al., 1979; Sugiura, 1996; Andrew, 2010). From there, they project via the spinothalamic tract to posterior/basal ventral medial nucleus of the thalamus and onward to posterior insular

cortex (Andrew, 2010). In humans, CT afferents also appear to ascend via the spinothalamic tract to the brain (Foerster et al., 1932; Lahuerta et al., 1994).

Neuroimaging studies in adults have shown that CT-targeted pleasant touch is processed in the posterior insular cortex (Olausson et al., 2002, 2008; Björnsdotter et al., 2009) and the mid-anterior orbitofrontal cortex (Francis et al., 1999; Hua et al., 2008; Mc Glone et al., 2012). In addition, posterior superior temporal sulcus (pSTS) (Voos et al., 2013), medial prefrontal cortex/ dorsoanterior cingulate cortex (Hua et al., 2008; Lindgren et al., 2012) and amygdala (Gordon et al., 2013) have also been implicated in processing of CT-targeted pleasant touch. Björnsdotter et al. (2014) observed pSTS/MTG and left insular activation in children (5–13 years) and adolescents (14-17 years), similar to that seen in adults (25-35 years). Moreover, the researchers also reported putative sex differences in the brain processing of affective touch as observed by increased sensitivity of pSTS with age in response to gentle touch in females (and not males) (Björnsdotter et al., 2014). Tuulari et al. (2017) reported that neonatal (11-36 days of age) brain is responsive to gentle stroking as evidenced by activation in postcentral gyrus and posterior insular cortex. These results suggest that affective touch activates both somatosensory and socio-affective regions in the brain in infancy (Tuulari et al., 2017).

Previous NIRS studies in adults show that pleasant touch causes activation in the anterior prefrontal cortex (Kida and Shinohara, 2013a), right pSTS and dorsolateral prefrontal cortex (Bennett et al., 2014). It has been suggested by Kida and Shinohara that the critical point of developmental changes in the tactile affective system is between 6 and 10 months of age, as they observed that gentle touch caused bilateral activation of anterior prefrontal cortex in 10-month-old infants, but not 3-month-old and 6-month-old infants (Kida and Shinohara, 2013b). Jönsson et al., 2018 observed activation in middle temporal gyrus and insular cortex (but not somatosensory cortex) in response to affective touch in two-month-old infants (Jönsson et al., 2018). These studies enable a deeper understanding of brain processing of affective touch. However, there are limited to none studies on affective touch in toddlers, especially between the age group of 1-4 years.

### *2.5.4 Role of touch in parent-child interaction*

Research has indicated that mothers touch their children between 33 and 61 % of the total time they communicate with them (Stack & Muir, 1990; Aznar & Tenenbaum, 2016). Furthermore, infants' responses to tactile stimulation develop within the parent-child interaction (Dunn, 2004); and may evoke distinct responses from the caregivers, thereby influencing the quality of parent-child interac-

tions (Mammen et al., 2016). For example, infants' atypical responses to touch have been linked with lower parental responsivity and higher parental stress (Degangi et al., 1997; Dunn, 2004; Epstein et al., 2008; Ben-Sasson et al., 2013). Since, touch is such an important aspect of parent-child interaction, it is essential to understand the processing of touch in children.

## 2.6 Summary of the literature review

Emotional speech has been considered a fundamental means of communicating emotions and has been investigated in children (Grossmann et al., 2010a; Blasi et al., 2011; Zhang et al., 2017). Nonetheless, there are scanty studies on how different emotions from speech are processed in two-month-old infants and whether the processing of emotional speech is associated with the maternal psychological distress during pregnancy. Additionally, there are no reported studies on whether the perceived maternal pregnancy-related anxiety symptoms at different time points of gestation are related with the emotional speech processing in infants. Although, affective touch is important for socio-emotional development of infants (Field, 1988; Greenough, 1990; Hertenstein and Campos, 2001; Stack, 2001; Hertenstein, 2002) and has been reported to decrease infants' physiological reactivity to stress (Feldman & Eidelman, 2003, 2004; Feldman et al., 2010); nevertheless there is a gap in the literature on how affective touch is processed in toddlers.

# 3 AIMS OF THE STUDY

The main purpose of this thesis was to contribute to the knowledge of emotional processing in the developing brain of young children. Furthermore, this thesis explores the association of emotional speech processing in infants with maternal psychological distress symptoms in the form of pregnancy-related anxiety.

The specific aims of the studies included in the thesis were:

I. To examine emotional processing in infants and children up to two years of age by a systematic review of NIRS studies (Study I).

II. To investigate how different types of emotional speech (happy, angry, sad and neutral) are processed in two-month-old infants using Diffuse Optical Tomography (Study II). Based on previous literature (please see sections 2.3.2 and sections 2.3.3 of Chapter 2), we hypothesized that speech would activate auditory cortex of the infants and different brain regions would be involved in processing different emotions from speech.

III. To determine whether maternal prenatal pregnancy-related anxiety associates with two-month-old infants' hemodynamic brain responses to emotional speech (Study III). Since, maternal anxiety during pregnancy has been reportedly associated with emotional problems in children (Martin et al., 1999; O'Connor et al., 2002; 2003; Van den Bergh et al., 2004) and changes in the auditory attention in the offspring (Harvinson et al., 2009; Hunter et al., 2012; Otte et al., 2015; Van den Huevel et al., 2015); we hypothesized that maternal pregnancy-related anxiety would be associated with child's processing of emotions from speech.

IV. To investigate how affective touch is processed in two-year old children using DOT (Study IV). Our hypothesis was that affective touch would activate more socio-emotional brain regions of children than non-affective touch, since affective touch has seen observed to activate somatosensory and socio-affective regions in the brain in infancy (Björnsdotter et al., 2014; Tuulari et al., 2017).

# 4 MATERIALS AND METHODS

## 4.1 Ethical considerations

All the studies included in this thesis were conducted in accordance with the Declaration of Helsinki. The Ethical Approvals for the studies II, III and IV were granted by the Joint Ethics Committee of the University of Turku and the Hospital District of Southwest Finland. The participant families were given oral and written information about the studies prior to the measurements. The parents signed an informed consent on the behalf of their children.

## 4.2 Participants and inclusion criteria

For **Study I**, we conducted a systematic review from reported 50 NIRS articles about emotional processing using external sensory stimuli in infants and children up to 2 years of age. For **Studies II-IV**, the participants were taken from the FinnBrain Birth Cohort Study which is a pregnancy cohort in Turku, Southwest Finland that aims to study the effects of prenatal stress on child neurodevelopment and health and identify biomarkers for later psychiatric and somatic illnesses (Karlsson et al., 2018).

For **Study II**, the study population consisted of 21 healthy infants between 6 and 10 weeks of age (9 females, mean age 55 days ± 9 days S.D.) that were born between June 2012 and October 2014 to the mothers participating in the FinnBrain Birth Cohort Study (Table 2).

For **Study III,** the study sample consisted of 19 infants drawn out of the 21 infants in **Study II** whose mothers had completed the pregnancy-related anxiety questionnaire at gestational weeks 24 and 34 during pregnancy (for details on questionnaire please see section 4.3.4). Thus, the study participants consisted of 19 infants (8 females, mean age 55 days ± 9 days S.D.) and their mothers with a mean age of 31 years (± 5 years S.D.) at the time of the measurement of their infants (Table 3).

For **Study IV,** the study population comprised of randomly selected 17 healthy two-year-old children (8 females, mean age 760 days ± 26 days S.D.) born to the families participating in the FinnBrain Birth Cohort Study in the time period between January and April 2014. Other inclusion criteria were children born full-term (36-42 weeks of gestation) with no history of medical, neurological or psychiatric disorders.

**Table 2 Characteristics of the children included in Study II and Study IV**

| | Study II (N = 21) | | Study IV (N = 17) | |
|---|---|---|---|---|
| | Median | Range | Median | Range |
| Age at measurement calculated from term (days) | 54.0 | 27 – 74 | 756.0 | 708-800 |
| Age at measurement calculated from the birthdate (days) | 52.0 | 43 – 71 | 752.0 | 734-786 |
| Gestational weeks at birth | 39.9 | 37 – 42 | 40.6 | 36-42 |
| Head circumference of the child at birth (cm) | 38.5 | 33 – 42 | 35.5 | 33-38 |
| Birth weight (g) | 3500.0 | 2525 – 4175 | 3680 | 2885-4900 |
| Birth height (cm) | 51.0 | 47 – 54 | 52 | 47-56 |
| Maternal age at measurement (years) | 32.1 | 21 – 37 | 36.0 | 23-46 |

**Table 3 Characteristics of the mother-infant dyad sample participants included in Study III. This table also appears in the original publication of Study III.**

| | | Median | Range |
|---|---|---|---|
| Infants (N = 19) | Age at measurement calculated from the birthdate (days) | 53 | 43 - 71 |
| | Head circumference at birth (cm) | 38.5 | 33.0 – 41.9 |
| | Birth weight (g) | 3500 | 2525 – 4175 |
| | Birth height (cm) | 51 | 47 – 54 |
| Mothers (N = 19) | Maternal age at measurement (years) | 32.1 | 21.4 – 37.3 |
| | Maternal Body Mass Index (BMI) | 22.5 | 19.5 – 35.4 |
| | Gestational weeks at birth | 39.7 | 37.3 – 41.9 |
| | PRAQ-R2 at gestational week 24 | 20.0 | 10.0 – 45.0 |
| | PRAQ-R2 at gestational week 34 (N = 18) | 20.0 | 13.0 – 40.0 |

## 4.3 Measurement session and experimental design

### *4.3.1 Study I: Systematic review*

For Study I, an extensive literature search was conducted in the PUBMED, the WEB of SCIENCE and EMBASE databases using the following medical subject headings (MeSH) terms and keywords: (NIRS OR fNIRS) AND (infants OR newborns OR children) AND (brain OR neuroimaging). Thereafter, we removed the duplicates, studies that were written in languages other than English, done in species other than humans, and performed in adults or children more than 2 years of age. In addition, we also excluded studies using non-emotional sensory stimuli, review articles, abstracts for presentations and case-reports. Thus, we collected a total of 50 articles for the review.

### *4.3.2 Study II: Emotional speech*

In Study III, we investigated how the two-month-old infants' brains process different types of emotional speech. The measurements were carried out in a room

with dimmed ambient lighting in the afternoon (Noon to 6 pm), since it was the preferred time for families. During the session, the mother was sitting on a comfortable chair and the infant was lying on the mother's lap in order to create a secure environment for the infant.

The emotional speech stimuli consisted of 11-second blocks of four recorded phrases that were spoken in happy, sad, angry or neutral voice in Finnish by an actress. There was different content but the same emotion within each block, and a rest period of 20 s to 30 s between two consecutive blocks (Kostilainen et al., 2018). One to three runs of 25 min duration were measured for each infant. These stimuli were presented using a computer running presentation software (Neurobehavioral Systems, USA) and a loudspeaker, with a sound intensity of approximately 65 dB and at an approximate distance of two meters from the infant. Concurrently, the cortical responses to the emotional speech, as measured by HbT concentration changes over left temporal cortex of infants, were recorded using HD-DOT.

### *4.3.3 Study III: Maternal questionnaire data and emotional speech*

In Study III, we explored the association between maternal pregnancy-related anxiety and infant emotional speech processing. During gestational weeks 24 and 34, we collected maternal self-reported symptom scores from postal and electronic forms of the Pregnancy-Related Anxiety Questionnaire-Revised 2$^{nd}$ version (PRAQ-R2), which is revised for pregnant women regardless of parity. Pregnancy-Related Anxiety Questionnaire-Revised (PRAQ-R) is a commonly used measure to assess and identify pregnancy-related anxiety in pregnant women (Huizink et al., 2002, 2003 & 2016). Previous studies have shown that the assessed pregnancy-related anxiety by PRAQ-R can be mostly differentiated from generalized anxiety; however, the two do influence each other during pregnancy (Huizink et al., 2002, 2003, 2014, 2016; Reck et al., 2013).

PRAQ-R2 is composed of 10 items rating from 1 to 5, and the total sum score ranges between 10-50 (Huizink et al., 2016; Nolvi et al., 2016; Karlsson et al., 2018). The PRAQ-R2 is composed of questions that reflect: *Fear of giving birth, Worries about Bearing a Physically or Mentally Handicapped Child, and Concern about Own Appearance*. Table 4 shows the English version of PRAQ-R2 which was used in study II. Thereafter, we correlated the maternal questionnaire data with their two-month-old infants' brain responses to emotional speech that were recorded in Study II.

**Table 4: English version of PRAQ-R2 questionnaire used in Study III. Answer categories: 1 = Absolutely not relevant, 2 = Hardly ever relevant, 3 = Sometimes relevant, 4 = reasonably relevant and 5 = Very relevant.**

| | |
|---|---|
| 1. I am anxious about the delivery | 1 2 3 4 5 |
| 2. I am worried about the pain of contractions and the pain during delivery | 1 2 3 4 5 |
| 3. I am worried about the fact that I shall not regain my figure after delivery. | 1 2 3 4 5 |
| 4. I sometimes think that our child will be in poor health or will be prone to illnesses. | 1 2 3 4 5 |
| 5. I am concerned about my unattractive appearance. | 1 2 3 4 5 |
| 6. I am worried about not being able to control myself during labour and fear that I will scream. | 1 2 3 4 5 |
| 7. I am worried about my enormous weight gain. | 1 2 3 4 5 |
| 8. I am afraid the baby will be mentally handicapped or will suffer from brain damage. | 1 2 3 4 5 |
| 9. I am afraid our baby will be stillborn, or will die during or immediately after delivery. | 1 2 3 4 5 |
| 10. I am afraid that our baby will suffer from a physical defect or worry that something will be physically wrong with the baby. | 1 2 3 4 5 |

### *4.3.4 Study IV: Skin stroking*

In Study IV, we investigated how the two-year-old children's brains process affective and non-affective (or discriminative) touch. The measurements were carried out in a room with dimmed ambient lighting in the afternoon (Noon to 6 pm), as it was the most convenient time for the families. Prior to the neuroimaging session, the child was encouraged to play for approximately 10 min until they were comfortable with the surroundings. During the session, the parent was asked to sit on a comfortable chair holding the child on their lap while the child was encouraged to watch videos of a neutral cartoon, to help motivate the child to sit still for the entire course of the measurement session.

A trained experimenter (AM) manually stroked the child's right dorsal forearm skin in a proximal to distal fashion using a hand-held soft brush. Affective touch was studied using slow brushing with a single stroke at an approximate speed of 3 cm/s whereas non-affective touch was studied using fast brushing with four to five strokes at an approx. speed of 30 cm/s. An average of 59 stimuli (30 slow and 29 fast) were presented per child in a randomized, counter-balanced order in an event-related design, where the stimulus was applied for 2 seconds, with an average inter-stimulus interval of 31 seconds. Simultaneously, the cortical responses to brushing, as measured by concentration changes in the total hemoglobin (HbT), over left fronto-temporal cortex of children were recorded using high-density diffuse optical tomography (HD-DOT).

## 4.4 Instrumentation and signal processing

### *4.4.1 Instrument*

The cortical activation in Studies II-IV was studied using 16-channel DOT instrument built at Aalto University (Nissilä et al., 2002; Nissilä et al., 2005). The instrument was based on the frequency-domain technique of NIRS, which uses intensity-modulated (100 MHz) light to determine the amplitude and phase shift of the transmitted photon-density wave (Kotilahti, 2015). We used a flexible silicone (Accutrans, Ultronics/Coltène) based high-density fiberoptic probe with embedded optodes (15 source fibers and 15 detector fiber bundles). The probe was placed over the left frontotemporal cortex of the children (Fig. 3), as previous research highlights involvement of left hemisphere in processing touch (e.g., Björnsdotter et al., 2014; Jönsson et al., 2018) and speech (e.g., Blasi et al., 2011; Kotilahti et al., 2010).

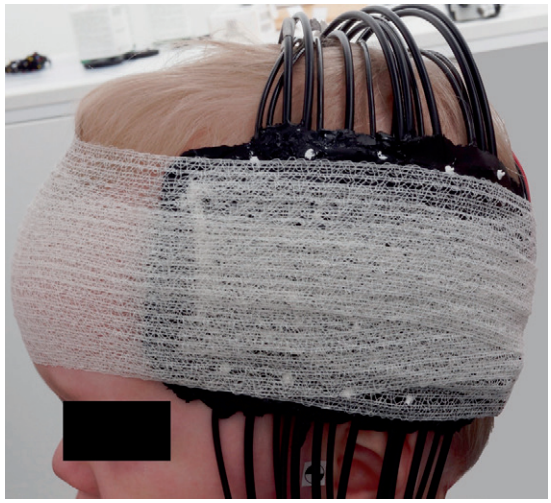

**Figure 3. The fiber-optic measurement probe was wrapped around the child's head with self-adhesive bandage. The visible landmarks and extra facial points help to register the optode locations to the head surface. Picture taken by Ilkka Nissilä during actual measurement for study IV.**

During the measurement session for Studies II-IV, we placed a colored glass pearl mesh on the child's head and black and white stickers (markers) on the child's left and right pre-auricular regions, nasion, cheek and chin (Fig. 4). This was done to facilitate later determination of the probe position and the field of view (FOV). Thereafter, five to seven pairs of pictures of the child were taken from different orientations using a stereo camera setup. This was done to create three-dimensional (3D) models of the child's head for locating the probe position relative to the landmarks. Subsequently, the probe was placed over the left frontotemporal cortex of the child by wrapping a self-adhesive bandage around the child's head. Finally, the entire measurement session was video recorded to help in the detection of motion artifacts due to the movement of the child.

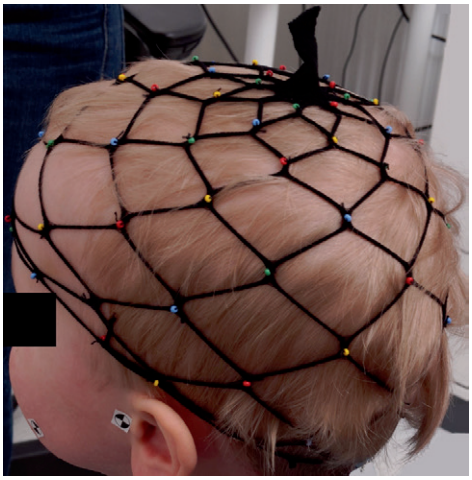

**Figure 4. A two-year-old child in study IV wearing the pearl mesh. The locations of the pearls, and the landmarks and extra facial points marked with stickers are reconstructed with two-camera photogrammetry. 60 pearls on average were reconstructed for each subject. Picture taken by Ilkka Nissilä.**

### *4.4.2 Signal processing*

The optode positions obtained from the 3D models from the photogrammetry were projected onto the surface of a representative MR image (e.g., Fig. 5). For studies II and III, a representative 1.5-month-old infant's MR image was manually segmented into tissue types and photogrammetry marker coordinates were used to scale the common model for each child. For study IV, we used a published age-appropriate MR template from Shi et al. (2011) that included segmentation of cerebrospinal fluid, gray matter and white matter, and an averaged intensity image that we used for manually segmenting a combined scalp and skull layer.

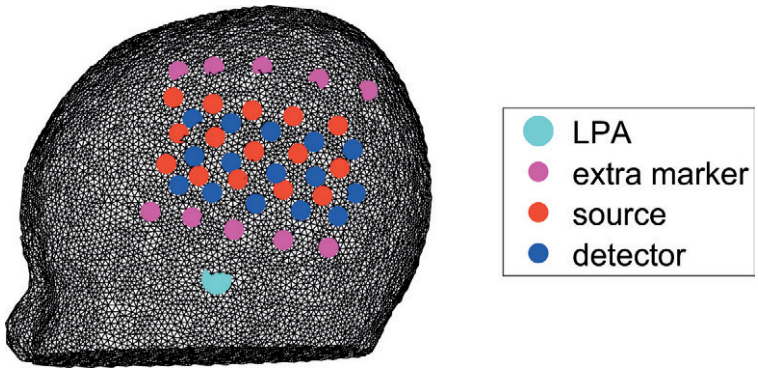


**Figure 5. The probe layout visualized on the head surface. LPA = left pre-auricular point. Since the bandage does not cover all of the extra markers, we reconstructed them (along with landmarks and facial points) with photogrammetry to guide the interpolation of the source and detector locations. The triangular surface mesh was created with iso2mesh-toolbox [http://iso2mesh.sourceforge.net/cgi-bin/index.cgi]. This was the deformed model for one of the subjects, so the template by Shi et al. had been registered to the photogrammetry target points. Figure created and displayed by the permission of Pauliina Hirvi author of *Generating optical head models for diffuse optical tomography of the child brain*, Master's thesis, Aalto University School of Science, 2019.**

After segmentation of the MR image, we simulated light propagation into the different tissues of the head using Monte Carlo method for photon propagation (Heiskala et al., 2007). These simulations were performed on the Monte Carlo eXtreme (MCX) open source software (Fang et al., 2009) on a NVIDIA Tesla K80 GPU-card. This was done to measure the sensitivities to changes in the absorption coefficient corresponding to each source-detector pair. For studies II and III, we used the data from source-detector pairs with separation under 45 mm, whereas for study II, we used the data from source-detector pairs with separation under 50 mm. The measurement FOV was set to include the voxels where the relative sensitivity was greater than 0.001 in at least seven subjects. The number of gray matter voxels within the FOV of the probe was $98\times10^3$ and in our experience, our imaging method is able to delineate approximately regions of 1 $cm^3$ from each other. Therefore, the correction factor for number of regions was 98. The number of source-detector pairs for which SDS between15 mm and 50 mm was 145. The average of these two factors was 120, which was later used as the correction factor in the voxel-based statistical analysis.

We used the modulation amplitude of the transmitted photon-wave as the optical signal in Studies II-IV. First, we removed the signal drift due to background physiology, optode-contact variations and spontaneous slow hemodynamic oscillations (Obrieg et al., 2000) by using a high-pass filter (-3 dB cutoff frequency at 0.007 Hz). Next, we analyzed the video recordings of the measurement session to determine the data with head movements, limb movements or crying. In addition, the motion artifacts were detected from a visually selected threshold, i.e., when the difference between the minimum and maximum of the filtered optical amplitude signal exceeded six times the standard deviation of the amplitude signal. After the removal of motion artifacts, the signal was averaged using deconvolution and the source-detector pairs that were observed to have a low signal-to-noise ratio were removed from the data analysis. Finally, the changes in the measured optical signal were converted into the concentration changes of HbT using the Modified Beer Lambert's law (Cope, 1991; Boas et al., 2001; Kotilahti, 2015).

## 4.5 Statistical analysis

**Study II**: To investigate responses to emotional speech in two-month-old infants, we used three analysis methods, i.e, the global approach, voxel-based clustering analysis and ROI-based-analysis. In the global approach, we averaged the HbT responses over all gray matter voxels (GM) within the FOV in the time window from 2 s to 18 s from stimulus onset. We performed two types of statistical tests: 1) Student's t-test: Here, we averaged the responses to all four emotional speech conditions and compared the resulting average with zero calculated across all the participants and 2) analysis of variance (ANOVA): This was done to investigate whether there were any statistically significant differences between the brain responses to different emotions. Tukey-Kramer post hoc test was used to determine which conditions differ from each other significantly, if ANOVA rejected the null hypothesis that all conditions come from the same mean. In addition, we tested if there was any significant response to each of the stimuli as compared to the baseline.

For the voxel-based clustering analysis, we looked for the regions with greatest statistical significance to the stimuli. Those regions were included in which the voxel-wise statistical significance was $p < 0.001$. In the next step, each region was expanded to include neighboring voxels that passed $p < 0.0033$ and $p < 0.01$. The regions that were separate at the higher significance level but merged at a lower significance levels were considered as one cluster. For the voxel-based clustering, we conducted: 1) Student's T-test: To compare the average across all

conditions and zero. 2) ANOVA: To compare the brain responses between the different conditions, and 3) comparison between each of the stimuli with baseline averaged within the window from -1s to 0s relative to stimulus train onset. The Bonferroni method was used to correct for multiple comparisons.

For the ROI-based analysis, we identified six regions of interest (ROIs) on the left hemisphere for our study (Fig. 6). The selection of these ROIs was based on previous studies showing activation in these brain regions in adults during speech perception and emotional processing (Morris et al., 1999; Specht & Reul, 2003; Johnstone et al., 2006; Liebenthal et al., 2010; Ethofer et al., 2011; Oh et al., 2014). ROIs were in anterior Superior Temporal Sulcus (aSTS), in Superior Temporal Gyrus (STG), in Inferior Frontal Gyrus (IFG), in left anterior Insula, in mid-Insula, and in posterior STS (pSTS). We calculated the mean HbT response values over two time windows, 4 to 8s and 4 to 14s. Thereafter, pairwise Student's t test was used to calculate the difference between the mean HbT value within the selected time window and the mean of the baseline, as well as the difference between slow and fast brushing. The Bonferroni method was used to correct for multiple comparisons (with a correction factor of 6).

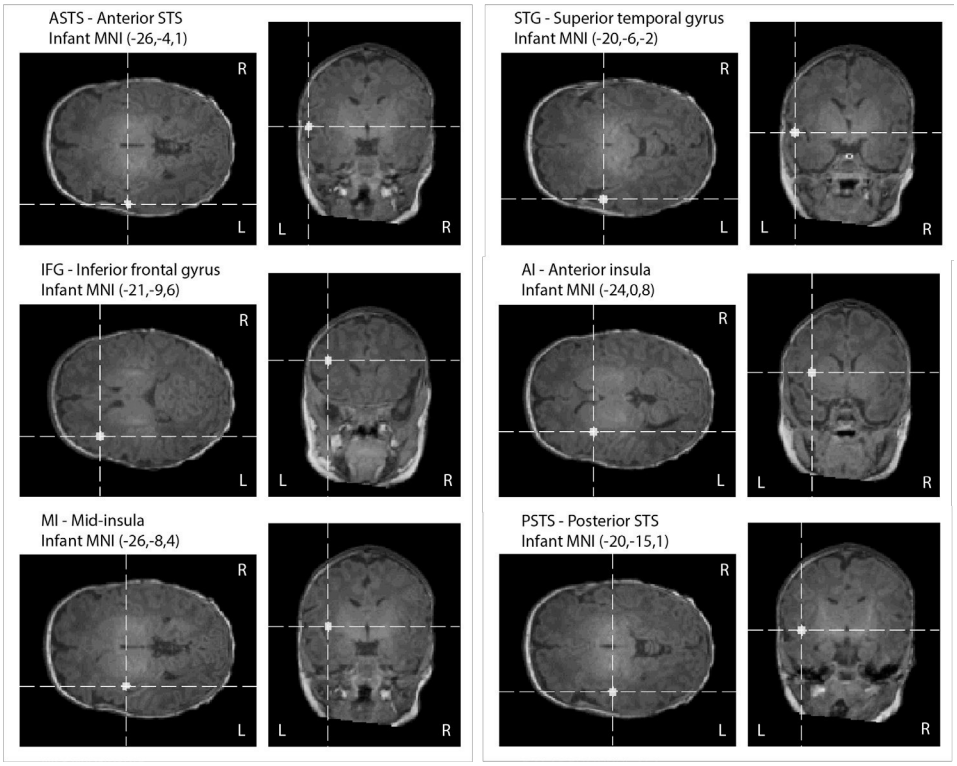


**Figure 6. Locations of the regions of interest (ROIs) used in the study II and III. The figure appears in the original publication of studies II and III.**

**Study III**: To investigate the association between the infant cortical responses to emotional speech and the maternal pregnancy-related anxiety symptom scores, we conducted ROI-based analysis as well as voxel-based clustering analysis. For the ROI-based analysis, the ROIs were the same six ROIs that were selected for study III (Figure 6) and HbT values within the time window from 2s to 18s from stimulus train onset for voxels within the ROI were averaged and Spearman's rank correlation coefficients (ρ) were calculated between the maternal PRAQ-R2 questionnaire scores and the HbT response for each emotional speech condition. The Bonferroni method was used to correct for multiple comparisons (with a correction factor of 6).

For voxel-based clustering, within the FOV, the adjacent voxels with $p < 0.001$ were combined into clusters and then the voxel response values within the cluster were averaged. We also included the adjacent voxels with $p < 0.0033$ and finally $p < 0.01$ in the cluster. The HbT response value was calculated by averaging the time course from 2 s to 18 s post stimulus train onset. Subsequently, cluster-level Spearman's rank correlation coefficients (ρ) were calculated between the maternal PRAQ-R2 questionnaire scores and the infant HbT responses for each emotional speech condition for each voxel within the FOV. Cluster-level p-values were calculated for each of the voxel-level p-value thresholds and the extent of the cluster was decided based on the lowest cluster-wise p-value. Multiple comparison correction using the Bonferroni method (with a correction factor of 120) was applied to the cluster p-value.

**Study IV**: We carried out two analyses approach, i.e. region-of-interest (ROI) based analysis and voxel-based clustering approach. For the ROI-based analysis, we identified 16 brain regions from the two-year-old infant Automated Anatomical Labeling (AAL) template by Shi et al., 2011. These brain regions were those for whom at least 30% of the volume of the AAL region was within the FOV for minimum seven subjects. The tested regions were: AAL 1 (Precentral gyrus left), AAL 7 (Middle frontal gyrus left), AAL 11 (Inferior frontal gyrus (opercular) left), AAL 13 (Inferior frontal gyrus (triangular) left), AAL 17 (Rolandic operculum left), AAL 51 (Middle occipital gyrus left), AAL 53 (Inferior occipital gyrus left), AAL 55 (Fusiform gyrus left), AAL 57 (Postcentral gyrus left), AAL 61 (Inferior parietal lobule left), AAL 63 (Supramarginal gyrus left), AAL 65 (Angular gyrus left), AAL 81 (Superior temporal gyrus left), AAL 83 (Temporal pole (superior) left), AAL 85 (Middle temporal gyrus left), and AAL 89 (inferior temporal gyrus left). For all the 16 regions, we averaged the gray matter voxels within the FOV and with their corresponding AAL number. Next, we selected two time windows, 4 to 8s and 4 to 14s, in which the mean HbT response values were calculated. Thereafter, pairwise Student's t-test was used to calculate the difference between the mean HbT response to slow and fast brushing within the

selected time window and the mean of the baseline. The Bonferroni method was used to correct for multiple comparisons with correction factor of 16, which was based on the number of regions tested.

In the voxel-based clustering approach, we searched for the gray matter voxels within the FOV and combined adjacent gray matter voxels that satisfy $p < 0.001$ into clusters and thereafter, calculated the cluster average HbT response for each condition. The voxel-level threshold was then increased to $p = 0.033$ and $p = 0.01$ and the clusters were extended to include these additional adjacent voxels. The cluster statistical significance was compared between three voxel-wise significance levels (0.001, 0.033 and 0.01) and the cluster extent was determined based on the smallest p-value. The cluster-wise averages were compared between slow brushing vs. baseline, fast brushing vs. baseline and slow vs. fast brushing using Student's t test. In the clustering analysis, we calculated the mean response value as average within the time window [4s, 14s] post stimulus onset. The Bonferroni method was used to correct for multiple comparisons (correction factor = 120).

# 5 RESULTS

## 5.1 Study I

To examine emotional processing in children under two years of age as measured by NIRS, we performed a systematic review of previous NIRS studies done (till January 8, 2018). Bilateral temporal activation has been reported in response to emotional stimuli in children in majority of NIRS studies, irrespective of which type of emotional stimuli was used. This finding indicates that NIRS is a useful modality to assess bitemporal cortical activation to emotional stimuli in children (Original publication I table 2, 3 and 4).

Moreover, the most commonly used stimuli in previous NIRS studies were visual (40%) followed by auditory (20%), audio-visual (14%), pain (12%), olfactory (8%) and tactile (6%). This result shows that touch has been the least common focus of interest in NIRS studies on emotion processing in children less than two years of age. In addition, we found that the majority of the studies (88%) were performed in infants while only limited studies (12%) were carried out in the age group between 1 to 2 years.

## 5.2 Study II

In order to explore the processing of different types of emotional speech stimuli in two-month-old infants, we recorded infant brain responses to pre-recorded happy, sad, angry or neutral speech using DOT.

**Results from the global approach**:

The time courses of the measured HbT responses for each of the four speech stimuli (happy, angry, sad and neutral) were averaged over the gray matter (GM) voxels within the field-of-view (FOV); excluding the voxels that were negative for either of the four emotional speech conditions. The response to neutral speech was negative and statistically significant (neutral < baseline; Fig. 3). Analysis of variance (ANOVA) and Tukey-Kramer post hoc test revealed that the response to happy speech was significantly greater than the response to neutral speech ($p = 0.01$, Fig. 7).

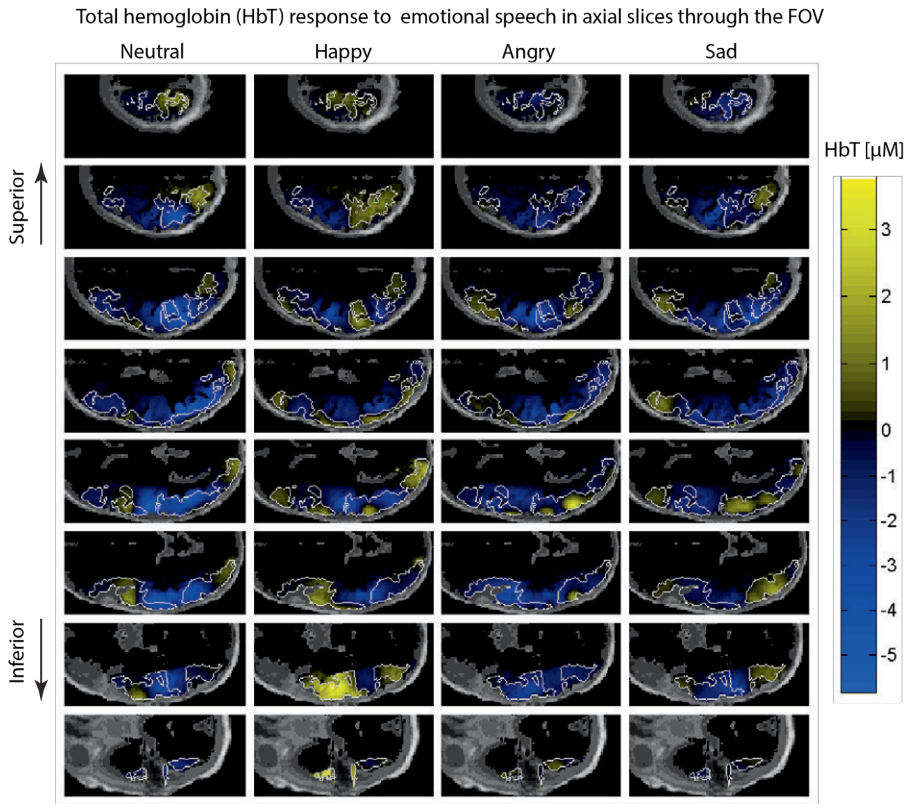


**Figure 7. Averaged HbT responses to emotional speech over the 21 subjects within the time window [2s, 18s] from stimulus onset in the left hemisphere. Each stimulus condition (emotional speech) is displayed as a column, and each row shows axial slices from top of the head to the bottom with 10 mm intervals. Warm colors (yellow) indicate an increase in total hemoglobin (HbT) response and cool colors (blue) indicate a decrease in HbT response to the stimulus. The scalp and skull are shown in dark gray. This figure appears in the original publication of study II.**

**Results from voxel-based clustering**: Emotional speech elicited a negative HbT response, averaged over all conditions and 21 infants, to emotional speech in a cluster in the left temporo-parietal cortex (Cluster 1 (C1); Fig. 8a-c). Neutral speech caused a negative HbT response in a cluster in the temporal cortex (Cluster 2 (C2); Fig. 8d-f). We did not find any clusters with a statistically significant response to angry or sad speech. Also, no clusters were observed with statistically significant differences between emotion-specific stimuli in the ANOVA test with multiple comparison corrections.

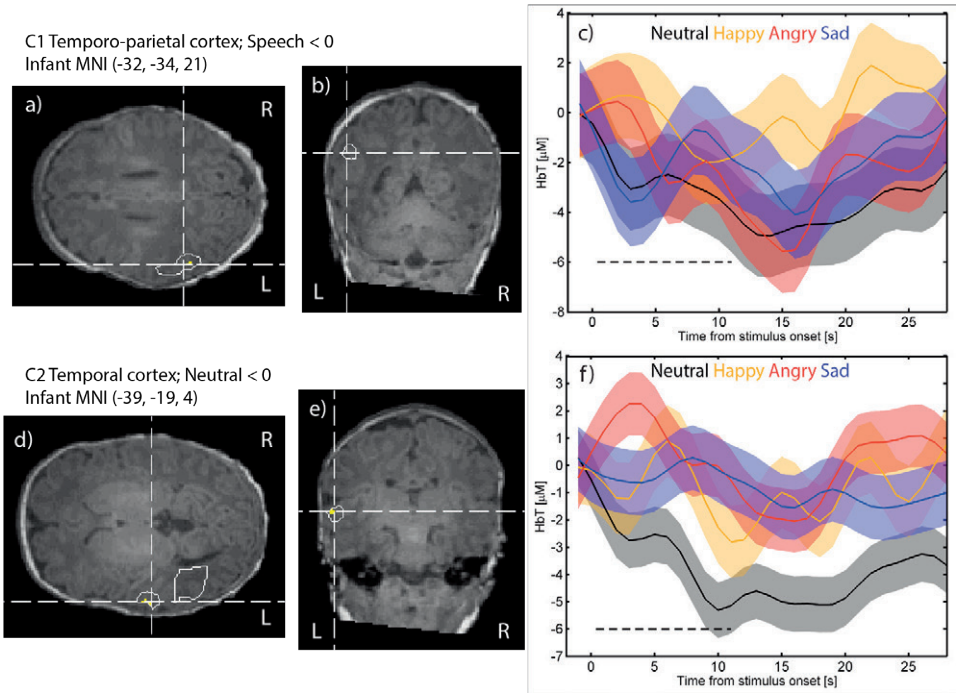


**Figure 8. Location of clusters showing a negative HbT response to emotional speech stimuli, with voxels that satisfy p < 0.001 marked in yellow and p = 0.01 marked with white contour line, and the corresponding HbT response time courses for each stimulus condition. Cluster 1 showed a significant negative response to speech in the temporo-parietal cortex (a-c); Cluster 2 elicited a significant negative response to neutral speech in the temporal cortex (d-f). Neutral speech is marked in black, happy speech in orange, angry speech in red and sad speech in blue. The shaded area shows the standard error mean (SEM). This figure appears in the original publication for study II.**

**Results from ROI-based analysis:** Analysis of variance (ANOVA) followed by Tukey-Kramer post hoc test found that neutral > angry in the anterior superior temporal sulcus (aSTS); happy > angry in the left STG; happy > angry and happy > neutral in the posterior STS (pSTS) (Table 5; Fig. 6). Further, we compared the responses in each of the ROIs with baseline using two-way Student's t-test. We found a negative HbT response to angry (compared to baseline) in the left aSTS, pSTS, STG, anterior and mid-insula (Table 5; Fig. 6). Interestingly, we also found a negative HbT response to happy (compared to baseline) in the left anterior insula.

**Table 5 Responses for each speech condition averaged over a time window of 2 to 18 seconds over ROIs, statistical significance of the difference between conditions based on ANOVA and Tukey-Kramer post hoc test and statistical significance of the response (compared to the baseline) based on two-way Student's t-test. * = p < 0.05 uncorrected; ** = p < 0.05 corrected for multiple comparisons for six regions. The coordinates are based on the UNC infant 0-1-2 template (Shi et al., 2011). aSTS: Anterior superior temporal sulcus, STG: Superior temporal gyrus, IFG: Inferior frontal gyrus, AI: Anterior insula, MI: Mid-insula and pSTS: Posterior superior temporal sulcus. This table appears in the original publication II.**

| | Approx. infant MNI coordinates | ANOVA p-value | Neutral HbT | Neutral p-value | Happy HbT | Happy p-value | Angry HbT | Angry p-value | Sad HbT | Sad p-value |
|---|---|---|---|---|---|---|---|---|---|---|
| aSTS | (-26,-4,1) | 0.036* neutral > angry* | 1.0 | 0.42 | 0.6 | 0.61 | -3.2 | $7.3\times10^{-3}$ ** angry < BL** | -1.1 | 0.28 |
| STG | (-20,-6,-2) | 0.025* happy > angry* | 0.4 | 0.74 | 1.0 | 0.42 | -3.8 | 0.013* angry < BL* | -0.6 | 0.52 |
| IFG | (-21,-9,-6) | 0.56 | -0.5 | 0.059 | -0.25 | 0.073 | -0.0 | 0.79 | -0.3 | 0.07 |
| AI | (-19,3,0) | 0.29 | 0.42 | 0.68 | -0.8 | 0.048 * happy < BL* | -2.0 | 0.012* angry < BL* | -1.3 | 0.20 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| MI | (-20, -7, 3) | 0.062 | 1.0 | 0.4 | 0.4 | 0.72 | -2.9 | $9.2\times10^{-3}$* angry < BL* | -1.2 | 0.28 |
| pSTS | (-20,-15,1) | 0.021* happy > angry*; happy > neutral* | 0.9 | 0.48 | 8.5 | 0.48 | -3.6 | $7.5\times10^{-3}$** angry < BL** | -0.9 | 0.32 |

**Summary:** We observed a positive HbT response to happy > neutral speech in the temporal and parietal cortices. Contrary to our expectations, we observed a negative HbT response to neutral speech and an average of emotional speech conditions in the left temporo-parietal cortex. Further, we found a positive HbT response to neutral > angry in the aSTS, happy > angry in the left pSTS and STG and happy > neutral in the pSTS. These results suggest that happy speech is preferentially processed over neutral speech and angry speech in two-month-old infants in the STS.

## 5.3 Study III

After investigating the two-month-old infant brain responses to emotional speech in study III, we wanted to explore if these infant brain responses would be associated with the psychological distress experienced by their mothers during the pregnancy in the form of pregnancy-related anxiety. To this end, we correlated our results from Study III with maternal self-reported pregnancy-related anxiety symptom scores collected using PRAQ-R2 questionnaire at gwks 24 and 34.

**Results from ROI-based analysis:** In Left Anterior STS (ROI 1), we found a negative correlation ($\rho = -0.61$) between maternal PRAQ-R2 scores at gwk 24 and the infant brain responses to sad speech. In addition, a negative correlation ($\rho = -0.59$) was observed between maternal PRAQ-R2 scores at gwk 24 and infant brain responses to sad speech in mid-insula (ROI 5) and Posterior STS (ROI 6)

(Table 6). No significant correlation was observed between infant brain responses to emotional stimuli and maternal PRAQ-R2 scores at gestational week 34.

**Table 6 Negative correlations between maternal pregnancy-specific anxiety symptoms (PRAQ-R2) at gestational week 24 and infant HbT responses to sad speech in the predefined regions of interest (ROIs). * = Statistical significance p < 0.05 Bonferroni corrected for the number of regions (6). gwk = gestational week. MNI =Montreal Neurological Institute.**

| Region name<br>Approximate adult MNI coordinates | Spearman's rank correlation coefficient | Brain response and correlated questionnaire measure p-value (Bonferroni corrected for 6 regions) |
|---|---|---|
| Anterior STS (ROI 1)<br>x = -57, y = 1, z = 0 | -0.61* | 0.033* |
| Mid-insula (ROI 5)<br>x = -42, y = 3, z = 9 | -0.59* | 0.046* |
| Posterior STS (ROI 6)<br>x = -52, y = -41, z = 10 | -0.59* | 0.049* |

**Results from voxel-Based Clustering:** We observed a cluster in the left STG (volume = 10.2 $cm^3$) in which the infant brain responses to sad speech correlated negatively (Spearman's rank correlation coefficient $\rho = -0.89$; $p = 4.3 \times 10^{-5}$) with the maternal PRAQ-R2 scores recorded at gwk 24 (Fig. 9).

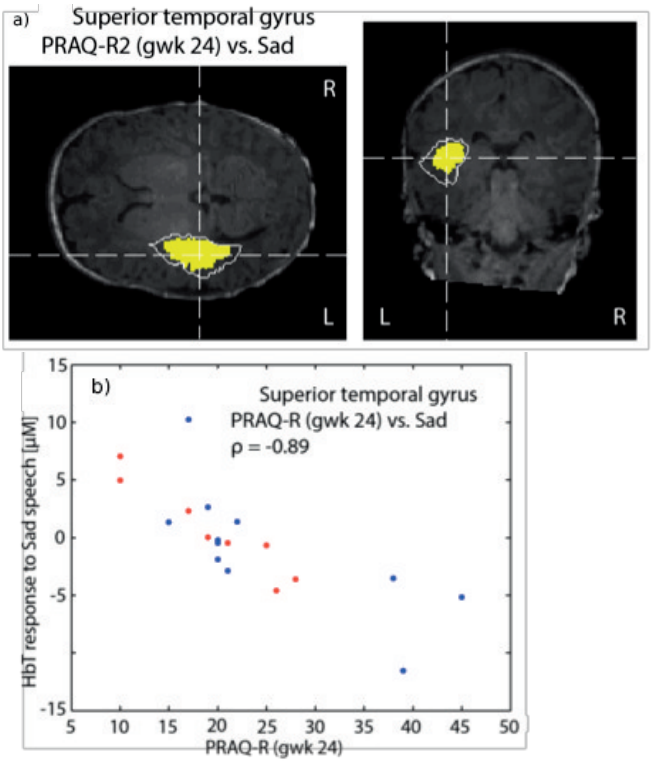


**Figure 9. Location of the cluster in superior temporal gyrus (a) with significant correlation (b) between maternal pregnancy-related anxiety symptom scores at gestational week 24 and infant brain responses to sad speech. Yellow solid area satisfies voxel-wise $p < 0.001$ and the region inside the white line satisfies $p < 0.01$ at the voxel level. Dashed lines cross at the center of gravity of the region. PRAQ-R2 = pregnancy-related anxiety questionnaire-revised 2nd version, gwk= gestational week, Red = female, blue = male. This figure appears in the manuscript of study III.**

**Summary**: We found that maternal pregnancy-related anxiety symptom scores collected at gwk 24 (and not at gwk 34) correlated with attenuated responses to sad speech in the left STG and mid-insula. These results suggest that maternal pregnancy-related anxiety associates with reduced processing of negative emotional stimuli (sad speech) in infant brain.

## 5.4 Study IV

To investigate the processing of affective touch in two-year old children, we observed the left fronto-temporal brain responses to slow brushing (relative to baseline and fast brushing) over right forearm using DOT. We expected that affective

touch would be processed in more socio-emotional brain regions of children than non-affective touch.

**Results from ROI-Based analysis**: We found a positive HbT response to slow brushing > baseline in the time window from 4 to 14 s in the opercular region of the left inferior frontal gyrus (IFG; Bonferroni corrected p = 0.0001); and in the left middle temporal gyrus (Bonferroni corrected p = 0.02). Moreover, the opercular region of the left IFG also showed a significant HbT response to slow > baseline in the shorter 4-8 s time window (Bonferroni corrected p = 0.03; Fig. 10). No significant results were observed for fast brushing vs. baseline or fast vs. slow brushing.

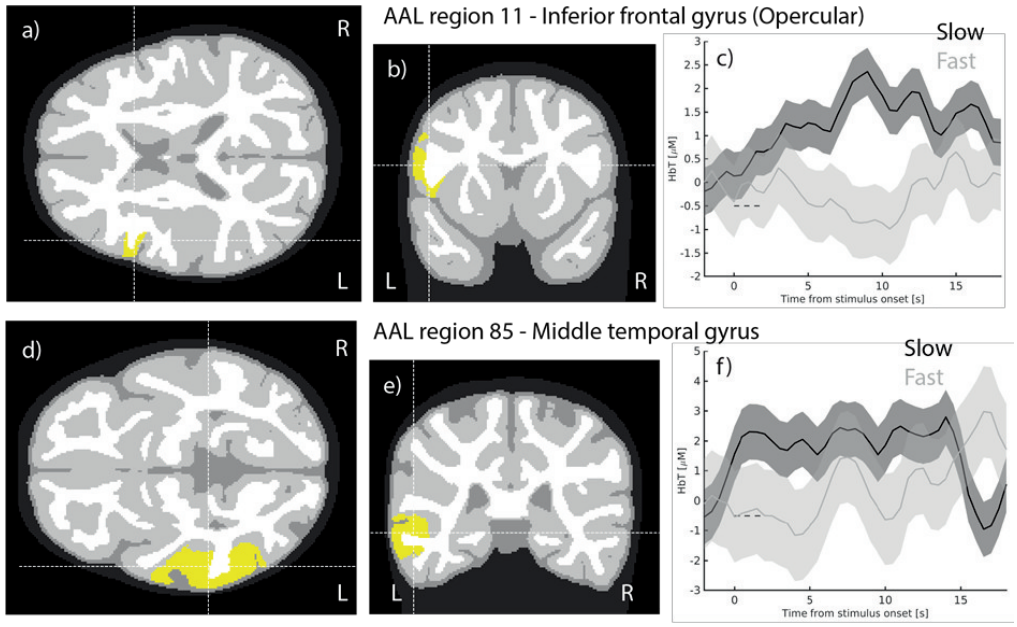


**Figure 10. Brain activation and time courses of HbT response in left inferior frontal gyrus (IFG) and left middle temporal gyrus to affective brushing. a-c) Opercular region of left IFG (AAL region 11) d-f) Left middle temporal gyrus (AAL region 85). In the HbT time courses, black line indicates slow brushing and dark gray line fast brushing; dashed line indicates the time of application of the touch stimulus and the shaded area represents standard error of mean. AAL: Automated Anatomical Labeling template was taken from Shi et al., 2011. This figure also appears in the original publication of study IV.**

**Results from clustering analysis:** In the time window from 4 to 14 s, we observed two clusters with a positive mean HbT response to slow brushing vs baseline; Cluster 1 was in the middle temporal gyrus (mean HbT: 7.3 μM; Bonferroni corrected p = 0.01) and Cluster 2 was mainly in the inferior frontal gyrus (mean

HbT: 2.6; Bonferroni corrected p= $5\times10^{-5}$; Fig. 11). No significant clusters were found for slow vs. fast or fast vs. baseline or fast vs slow.

**Summary:** Our results revealed that affective touch is likely processed in the contralateral IFG and middle temporal gyrus in two-year-old children. As these regions are key components of the "social brain", they play an important role in the positive affiliative bonding that occurs between parents and their children via affective touch.

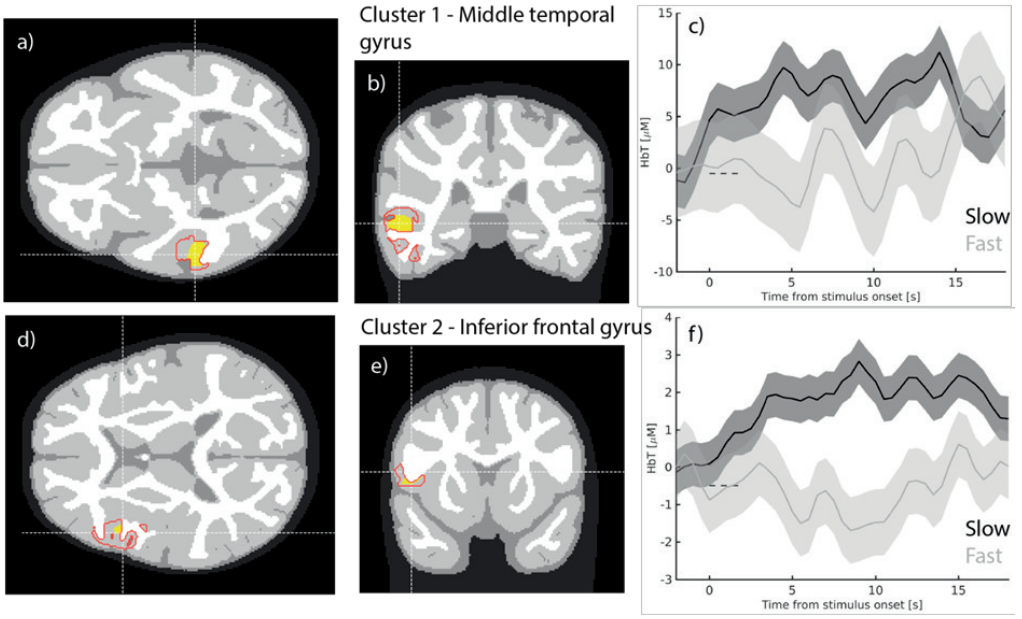


**Figure 11. Location of the clusters of activation and time courses of responses to slow and fast brushing in the clusters. a-c) Cluster 1 was located in the middle temporal gyrus; $p_{voxel} < 0.001$ indicated in yellow; $p_{voxel} = 0.01$ contour marked with red line. d-f) Cluster 2 was located in the inferior frontal gyrus. Black line indicates the response to slow brushing and dark gray line indicates the response to fast brushing; black dashed line indicates the time of application of the touch stimulus and the shaded area indicates standard error mean. This figure also appears in the original publication of study IV.**

# 6 DISCUSSION

The aim of this thesis was to broaden our understanding of emotional speech and affective touch processing in children using DOT. To this end, the thesis presented first the main findings from the previous literature of NIRS studies on emotion processing in infants and children up to two years of age. Second, it explored how different types of emotional speech (happy, sad, angry and neutral) are processed in two-month-old infants' brains. Third, it tested if the emotional speech processing in two-month-old infants' brains is associated with pregnancy-specific anxiety experienced by their mothers during pregnancy. Finally, it investigated whether affective and non-affective touch activates differential brain areas in two-year-old children.

## 6.1 Emotional processing studies in toddlers using NIRS (Study I)

Bilateral temporal cortical activation has been most commonly reported in response to emotional stimuli in small children by studies using NIRS, regardless of the type of stimuli involved used. Previous reviews of NIRS studies on prefrontal cortex activation in response to emotional stimuli have suggested that NIRS appears to be well-suited to measure prefrontal cortex activity in emotion research (Doi et al., 2013; Bendall et al., 2016). Our review supports the idea that NIRS is a useful tool for studying bilateral temporal cortical responses to emotional stimuli in children as well. Further, the most commonly used stimuli in emotion processing studies in children under 24 months by NIRS was visual (40%) followed by auditory (20%), audio-visual (14%), pain (12%), olfactory (8%) and tactile (6% stimuli). This result suggests that among the above-mentioned stimuli, touch is the least common focus of interest in studying emotion processing in small children, despite being one of the primary modes of bonding between children and caregivers. Our result is in contrast to the finding by a systematic review by Cristia et al. of 72 empirical fNIRS studies (on July 20, 2012) done in infants and children less than three years of age (Cristia et al., 2013). The researchers found that the most commonly used stimuli were language (25%), followed by auditory (13%), visual (12%), facial (11%) and motor, music, social and pain together comprised 3% (Cristia et al., 2013). The observed discrepancy in results might be due to the fact that we included 'facial' stimuli in the category of 'visual' stimuli', as facial expressions are a common way by which children interpret and convey their emotions to the caregivers. Another possibility is that we focused solely on the emotional stimuli and our review did not include children between two to three years of age (as compared to Cristia et al.).

Our review highlighted that the majority of NIRS studies on emotional processing were done in infants (88%) as compared to children in the age group of 1 to 2 years (12%). Our findings are similar to the findings by Cristia et al. who reported that out of the NIRS studies in children less than three years of age, 87% of them were in infants (Cristia et al., 2013). Our result highlights that the age group of children between one and two years of age is relatively less-studied in NIRS research on emotional processing. This may be due to the practical limitations of imaging toddlers as it is difficult to get their compliance for being immobile for the duration of the measurement session. Nevertheless, we think that using fiberless NIRS methods and designing future studies that sustain the child's interest for the duration of the measurement session can hopefully solve this problem.

## 6.2 Emotional speech processing in two-month-old infants (Study II)

To test the hypothesis that two-month-old infants can differentiate between emotions in speech, we used DOT to investigate two-month-old infants' processing of different types of emotional speech (happy, sad, angry or neutral speech). Our first result was a statistically significant positive HbT response to happy > neutral speech across the left temporal and parietal cortices in infants, with the largest contrast occurring in the anterior part of the temporal cortex. This result suggests that infant brains are able to discriminate positive emotions (e.g., happy speech) from neutral speech already at two months of age. Furthermore, we found that the positive HbT response to happy speech was relatively short in duration (peak response was at 4-5 s). This was in contrast to the longer HbT response (peak response at 14-15 s) to angry and neutral speech. Our finding implies that there might be strong habituation to happy speech in infants, most likely due to the familiarity of the positive stimuli in the postnatal environment. Importantly, our result suggests that the infants' preference to positive stimuli (e.g., happy speech) at this stage of development, as it helps them in social interaction and bonding with their caregivers (Farroni et al., 2005; 2007).

Our second result was that we found a greater response to neutral speech > angry speech in left anterior STS; happy speech > angry speech in the left posterior superior temporal sulcus (pSTS) and superior temporal gyrus (STG); happy speech > neutral speech in the pSTS. These findings highlight the key role of left STS in infant brain for differentiation of emotions from speech. Our findings are in line with the observations of Blasi et al. who observed that 3-7-month-old infants exhibited differential activation to adult non-speech vocalizations (emotionally neu-

tral, emotionally positive, and emotionally negative) in the anterior portion of left temporal cortex, similar to that seen in adults (Blasi et al., 2011).

Previous adult fMRI studies have reported STS activation in response to happy intonation of voice, which is similar to our finding of STS activation in response to happy speech in infants. For example, Wittfoth et al. reported left STG and left inferior frontal gyrus activation in adults in response to happy intonated sentences, although, expressing negative content. This result reveals that left STG plays an important role in processing happy prosody rather than happy semantic content from the speech (Wittfoth et al., 2010). Koelsch et al. reported greater response to joy-inducing music (compared to fear-inducing music) in the left (and right) transverse temporal gyrus in adults. These results imply that auditory cortex has regions that are involved in processing affective information from auditory stimuli in adults (Koelsch et al., 2018), similar to that seen in infants as observed from our study. Besides STS, Johnstone et al., also showed anterior and mid-insular activation in response to happy voice than angry voice (Johnstone et al., 2006). Altogether, our study augments and corroborates with the findings from previous studies showing the involvement of STS and insula in processing happy speech in infants at two-months of age.

We found a non-statistically significant positive HbT response to angry > neutral in the middle STS in response to angry speech. Similar to this finding, Grandjean et al. reported middle part of STS activation in adults in response to angry prosody in meaningless sentences (Grandjean et al., 2005). Additionally, we observed a negative HbT response to angry < baseline in aSTS, pSTS, STG, anterior insula and mid-insula, as well as happy < baseline in the anterior insula.

For neutral speech and the average of all speech conditions, contrary to our expectations, we found a statistically significant negative HbT response in the left temporo-parietal cortex. We think that this negative HbT responses is similar to the negative blood-oxygen-level dependent (BOLD) response which could be considered as a result of the attenuation of the normal functionality of the resting-state activity in the brain due to the temporary reallocation of resources during the performance of a task (Raichle & Mintun, 2006; Gusnard & Raichle, 2001; Raichle et al., 2001). Another possible, although less likely, explanation for these negative HbT responses could be due to a purely vascular effect called “vascular steal effect”, which refers to observed reduction of blood pressure, cerebral blood flow and volume in the areas that surround the area which shows stimulus-elicited activation and positive HbT response (Hayes & Huxtable, 2012; Tomasi et al., 2006; Weinand, 2000). A few recent studies have also found negative $HbO_2$ responses to auditory stimuli, such as, Gomez et al. to syllables in the left and right frontoparietal and temporal-perisylvian regions in newborns (Gomez et

al., 2014); and Grossmann et al. to happy > angry > neutral sounds in left temporal cortex in 5-month old infants (Grossmann et al., 2010b). In adults too, Bauernfeind et al. observed negative $HbO_2$ responses to pure tone auditory stimuli in the central and parietal regions of both hemispheres and positive $HbO_2$ responses in the middle temporal and frontal cortices (Bauernfeind et al., 2018). Nevertheless, further studies are needed to understand the mechanism behind these negative HbT responses observed in infants.

## 6.3 Maternal pregnancy-related anxiety and infant responses to emotional speech (Study III)

We tested the hypothesis that maternal pregnancy-related anxiety would be associated with the neuronal processing of emotional speech stimuli in two-month-old infants. This was done by correlating maternal self-reported symptom scores from pregnancy-related anxiety questionnaire second revised version (PRAQ-R2) at gwks 24 and 34, with infant hemodynamic responses measured using DOT to different types of emotional speech (happy, sad, angry or neutral speech). Our main result was that maternal pregnancy-related anxiety symptom scores collect-ed at gwk 24 (and not at gwk 34) correlated negatively with the HbT response to sad speech in the left STG (Spearman's rank correlation coefficient $\rho = -0.89$) and mid-insula ($\rho = -0.59$). Since, STS and insula are prominent brain regions involved in social cognitive processes (Frith & Frith, 2007; Blakemore, 2008), reduced processing of sad speech in these areas might be revealing the link between maternal pregnancy-specific anxiety symptoms and socio-emotional development of infants. However, what this means for the long-term socio-emotional development of children needs to be investigated in future longitudinal studies. Importantly, these results highlight the need for the development of ma-ternal stress reduction measures during pregnancy.

Our study reveals that maternal pregnancy-related anxiety symptoms at mid-point of pregnancy are associated with reduced responses to sad speech in infants. Our findings are in line with the developmental origins of behavior, health and disease (DOHAD) hypothesis, which proposes that intrauterine and maternal conditions during pregnancy may affect the neurodevelopmental pathways of the fetus and child (Van den Bergh, 2011; Gluckman et al., 2009; Räikkönen et al., 2011). We think that we observed the association between pregnancy-specific anxiety and infant responses to sad speech only in gestational week 24 (and not 34) because there might be different mechanisms underlying pregnancy-specific anxiety effects operating at different points of gestation. These effects likely depend

on genetics, the developmental stage of specific brain areas and connections, the stress system and the immune system (Van den Bergh et al., 2005b, 2017).

Our results support and extend the findings from recent studies depicting the association of maternal pregnancy-specific anxiety with neurocognitive outcomes in children. For example, Huizink et al. reported that pregnancy-specific anxiety at 27-28 weeks and maternal generalized anxiety at 15-17 weeks were associated with infant attention-regulation problems at 3 months and 8 months (Huizink et al., 2002, 2003). In contrast, high pregnancy-related anxiety in mothers at 16 weeks of gestation (but not later in gestation) was associated with lower scores on mental development index in infants at 12 months of age (Davis & Sandman, 2010). Similarly, Buss et al. reported that high pregnancy-specific anxiety at 19 weeks of gestation was associated with reduced grey matter volume in 6-9-year-old children (Buss et al., 2010). Altogether, these results suggest that high maternal pregnancy-specific anxiety during the second trimester of pregnancy affects the attention-regulation and neurocognitive outcomes of children.

Similarly, associations between maternal anxiety and emotional problems in children have been reported by earlier studies. For instance, Kataja et al. found that maternal anxiety symptoms in gwk 14 was associated with higher threat bias in infants (as reflected by probability of disengagement from fearful faces using eye-tracking), and remained significant even after controlling for maternal postnatal anxiety symptoms (Kataja et al., 2019). Maternal psychological distress at 1-16 weeks has been associated with negative emotionality of 5-year-old children (Martin et al., 1999). Maternal anxiety at gwk 32 appears to be a stronger predictor of behavioral/emotional problems in 4- and 7-year-olds, compared to anxiety at 18 weeks (O'Connor et al., 2002, 2003). Van den Bergh et al. found that maternal anxiety at gwks 12-22 weeks (and not anxiety at gwks 32-40 weeks) was a significant predictor of anxiety and externalizing problems in 8- to 9-year-old children and cognitive functioning at age 14-15 (Van den Bergh & Marconen, 2004; Van den Bergh et al., 2005a). Taking the above results together with our findings, it is possible that maternal generalized anxiety during first half of pregnancy is more associated with infant emotional responses, while pregnancy-related anxiety during the mid-point of pregnancy is more correlated with infant emotional responses. However, further research needs to be done to see if this hypothesis indeed holds true.

Fetal experience with auditory stimuli (such as mother's voice) in utero has been seen to have a profound effect on the newborns' responses to auditory stimuli (Sullivan et al., 2011; Fifer & Moon, 1994). According to Haan et al., frequent exposure of a particular emotional expression may result in a diminished response to that expression in infants (Haan et al., 2004). Thus, it is possible that

infants' attenuated response to sad speech indicates a blunted response to negative emotional expression (sad speech), as it might be a familiar stimulus for the infants from the perinatal environment. Nonetheless, further studies are needed to confirm this hypothesis to be the likely explanation behind the observed attenuated brain responses to sad speech in infants of mothers who perceived high pregnancy-related anxiety during gestation.

## 6.4 Affective touch processing in two-year-old children (Study IV)

We wanted to test the hypothesis that affective touch is processed differently as compared to non-affective touch in two-year-old children. In order to do so, we used DOT to examine two-year-old children's brain hemodynamic responses to slow brushing (as a proxy for affective touch) and fast brushing (as a proxy for non-affective touch). Our major finding was a significant positive HbT response in the opercular part of left IFG and left middle temporal gyrus to slow brushing compared to the baseline. This result reveals that affective touch is processed in left IFG and middle temporal gyrus in two-year-old children.

Our findings about the involvement of left IFG and middle temporal regions in processing affective touch are in line with the findings from recent NIRS studies (Pirazzoli et al., 2018; Jönsson et al. 2018; Bennett et al., 2014). Pirazzoli et al. observed that left IFG and posterior temporal regions were activated in response to affective touch on the upper arm in five-month-old infants. Furthermore, the researchers reported bilateral IFG and posterior STS-temporoparietal junction activation in response to non-affective touch (Pirazzoli et al., 2018). In contrast, we did not observe any significant HbT response in the left fronto-temporal cortex to fast brushing relative to the baseline or fast versus slow brushing.

One reason for the difference between our findings from that of Pirazzoli et al. might be the choice of stimuli: Pirazzoli et al. used gentle stroking at a speed of 3-10cm/s with human hand as a proxy for affective touch while they used stroking with a spoon at the same speed as a proxy for non-affective touch. As, affective touch, is known to be mediated by CT fibers that respond most optimally by a stroking velocity of 3-10cm/s and non-affective touch is usually mediated by A-beta fibers that respond at a faster velocity. Since, Pirazzoli et al. used the same speed as the stroking velocity for both affective and non-affective touch, it is hard to determine if the results obtained might be affected by the difference in temperature and the texture of the stimuli (human hand and spoon) (Pirazzoli et al., 2018). Another possibility might be the location of our probe, which was on the left frontotemporal cortex in our study as compared to bilateral inferior frontal and temporal cortices in Pirazzoli et al. Nevertheless, our results highlight

the specific role of left IFG in processing affective or social touch in two-year-old children.

Previous fMRI studies on affective touch processing have highlighted the role of frontal cortex in affective touch processing (Francis et al., 1999; Gordon et al., 2013; Olausson et al., 2002; Rolls et al., 2001; Voos et al., 2013). Björnsdotter et al. reported the activation of pSTS and left insula in response to affective touch in children (5–13 years) and adolescents (14–17 years), with the magnitude similar to that seen in adults (25–35 years). Although, they do report right FG activation in adolescents; interestingly, they did not find any frontal activation in response to affective touch in the children between 5 to 13 years of age (Björnsdotter et al., 2014). Adding to the literature, our result of left IFG sensitivity to affective touch in two-year-olds suggests that left IFG is particularly important in affective touch processing in younger children.

Our finding of involvement of left middle temporal regions in processing affective touch illustrates temporal brain responses to touch. This is in line with the findings from previous NIRS studies, such as Jönsson et al. that reported activation in the left middle temporal cortex and insula in response to affective touch in two-month-old infants (Jönsson et al., 2018). However, we did not detect any activation in the insula in our two-year-old participants and it might be because the relative sensitivity of NIRS to detect activation from deeper brain tissues such as insula decreases with age. Besides insula, right pSTS and dorsolateral prefrontal cortex activation has been observed in response to arm > palm touch in adults (Bennett et al., 2014). Also, few recent studies suggest that primary somatosensory cortex (S1) may be involved in processing affective touch (Gazzola et al., 2012; McCabe et. al., 2008; Tuulari et al., 2017). However, the location of our probe did not permit us to examine the right hemisphere, insula or areas situated outside the FOV, such as the S1, we cannot say whether these areas showed any activation in response to affective or non-affective touch. Therefore, further studies are needed to shed more light on the affective and non-affective touch responses in these brain regions.

## 6.5 Limitations

For the systematic review of emotional processing NIRS studies (**Study I**), as there is no consistent definition of the term “emotional stimuli” in the literature, we chose to include those studies that had used external sensory stimuli for eliciting the emotional responses in the subjects. Although, a meta-analysis of the studies would have provided more information on the topic, we found that it was

not possible due to the differences in the equipment used, measurement areas and the experimental designs in the included studies.

For **study II**, we could not clearly record and control for the awake/sleeping status of the infants, although it has been has been noted that the state of infants can affect speech processing (Dehaene-Lambertz et al., 2002). It was because the video quality of the measurement session was only sufficient to detect subject movement and not sleep / awake status of the infants due to the dim lighting in the room and wide angle of view of the video (which was chosen to include mother in the video). Nevertheless, future studies should take into account the state of the infants during the measurement session.

Another limitation of our study was that we did not include fearful speech in the study design. In retrospect, the use of fearful speech (along with sad and angry speech) would have provided important information about the emotional processing of negative stimuli in infants as well as its association with maternal pregnancy-related anxiety. However, we chose to only include angry and sad stimuli as proxy of negative emotions to have sufficient number of repetitions for stimuli of each condition in a realistic measurement time. Nonetheless, future studies would benefit from including fearful speech in their study designs. Also, small sample size was a limitation in our studies and future experiments should aim for a larger sample size.

For **study III**, we used self-reported questionnaire (PRAQ-R2) as a measure of pregnancy-specific anxiety in mothers. It has been suggested that perceived stress, as depicted by the questionnaires, is in part heritable, and that the heritability estimates depend on the specific questionnaire in account **(**Federenko et al., 2006). Therefore, when studying heritability of perceived stress, it is important to consider the specific questionnaire and genetic vulnerability into account. It is also worth noting, that the measurement reliability and validity of maternal psychological stress questionnaires is challenging given its subjective nature and individual differences in the regarding a situation stressful (Mcewen, 1993; Lobel, 1994; Dipietro, 2012). Since, maternal personality characteristics, such as trait anxiety, have been shown to be positively associated with perceived pregnancy-specific anxiety, therefore, it is likely that maternal personality traits influence the self-reported questionnaires (Pluess et al., 2010). Another limitation was the small sample size of mother-infant dyads and future studies should aim for a larger sample size. Furthermore, caution should be exercised in interpretation of the results, as we did not find a significant correlation between infant hemodynamic brain responses to emotional speech and PRAQ-R2 scores at gestational week 34.

Another limitation of our study would be that we did not measure the psychological distress symptoms in fathers. This was done to keep our focus on the effects of maternal pregnancy-specific anxiety on infant brain responses to emotional speech. Since, paternal depression may influence maternal perceived anxiety and parental stress (Vismara et al., 2016) and has been associated with negative child outcomes (Ramchandani et al., 2005; 2008; Tambelli et al., 2014); future studies should be done to disentangle the effects of paternal anxiety, maternal personality characteristics, measured prenatally, and the perceived maternal pregnancy-specific anxiety on the offspring outcomes.

For the hemodynamic responses to touch stimuli (**Study IV**), we measured brain responses to slow brushing as a proxy for affective touch, perceived pleasantness of which is considered to be mediated by CT fibers. To simulate real-world conditions, the touch stimulus was provided by an experimenter (instead of a robot), while the caregiver was holding the child in their lap. In addition, the subject-reported pleasantness of brushing stimuli delivered manually at 3 cm/s has been observed to be comparable to that of analogous stimulation delivered by a robot (Triscoli et al., 2013). Since, the caregiver was holding the child during the measurement session to make the child more comfortable, further studies are needed to study parent-child interactions in such studies, as it might also influence the perceived pleasantness of affective touch. Further, force and speed of stimulus delivery, and sex of the receiver may affect the perceived pleasantness of the tactile stimuli (Essick et al., 2010). Thus, it is still unclear whether the pleasantness perceived by touch can be viewed as a one-dimensional construct and further studies should take the above factors into account (Essick et al., 2010).

It is interesting to note that IFG activation has also been reported in response to motor action observation (Molnar-Szakacs et al., 2004; Peled-Avron et al., 2018). Subsequently, in theory, it is possible to consider that the motor component of brushing might influence IFG activation. However, in natural social interactions, the person being touched usually is aware of the person. Further, in our study, the non-affective touch constituted of 4-5 strokes as compared to a single stroke in the affective touch condition. Therefore, our finding of left IFG activation in response to affective touch more accurately reflects the pleasantness associated with the affective touch. Nonetheless, in our study, we cannot completely disentangle the effects of the child observing the experimenter's touch on their forearm and the pleasantness associated with the affective touch and further studies should take this into account.

During the entire measurement session, the child was watching videos of a neutral cartoon. Though, it is possible that watching the videos may have an effect

on the child's processing of touch stimuli, the choice was made to keep him or her to sit still for the measurement. Furthermore, it has been shown in previous studies with touch experiments on infants that silent videos capture the child's attention and improve the signal-to-noise ratio of measurement data (Fairhust et al., 2014; Miguel et al., 2017).

## 6.6 Clinical significance of the findings

The results reveal that two-month-old infants can already discriminate happy tone of voice from other emotions in speech in brain areas responsible for infant's socio-emotional development. This finding highlights the need to reinforce the importance of positive auditory stimuli in the infants' postnatal environment as it might affect their emotional development.

Not only postnatal, but also the prenatal environment seems to affect the infant responses to emotional stimuli. The results suggest that maternal pregnancy-specific anxiety symptoms are associated with decreased infant brain responses to sad speech. These findings encourage education to pregnant families about the effect of maternal pregnancy-specific anxiety on the infant brain.

The results reveal that affective touch is processed in the left IFG and left middle temporal gyrus in two-year-old children. As these regions are key components of the "social brain", involvement of the left IFG in affective touch processing in typically-developing children might act as groundwork for future studies in not only typically-developing children but also children with disrupted social perception, such as autism spectrum disorders (ASD).

# 7 CONCLUSIONS

The present thesis sheds some light on the emotional processing in children's brains and its association with maternal perceived pregnancy-related anxiety. Specifically, we used DOT to study two-month-old infants' hemodynamic brain responses to emotional speech, their correlation with maternal pregnancy-related anxiety symptoms and two-year-old children's brain responses to affective touch. We also presented results from the systematic review of emotional processing studies done using NIRS in infants and children up to two years of age.

The results from **Study II** illustrate that two-months-old infants preferentially process happy speech over other types of emotional speech (angry, sad and neutral speech) in left STS (a brain region involved in social and cognitive processes).

The results from **Study III** reveal that maternal pregnancy-related anxiety symptoms collected from pregnancy-related anxiety questionnaire (PRAQ-R2) during gwk 24 (and not gwk 34) associates with two-month-old infants' attenuated hemodynamic responses to sad speech in left STG and mid-insula. This study contributes to the literature by showing that infants' neuronal processing of emotional speech is correlated with their mothers' level of perceived pregnancy-related anxiety symptoms during mid-pregnancy. Thus, these results suggest that maternal perceived pregnancy-related anxiety might affect infant brain's emotional responses and therefore, necessitates the need for maternal stress reduction during pregnancy.

The results from **Study IV** show that affective touch applied on the right forearm of two-year-old children is processed in their left IFG and middle temporal gyrus. Since, these brain regions are key components of the "social brain", affective touch helps in forming social bonds between children and their caregivers. To the best of our knowledge, **Study IV** is the first reported functional neuroimaging study on affective touch processing in two-year-old children and thus, fills an important gap in the literature.

# 8 FUTURE DIRECTIONS

Future studies on emotional processing in children should aim to include children in the age range from 1 to 2 years as little is known about their emotional processing mechanisms. Furthermore, use of combined audiovisual stimuli in study designs should be aimed for, as in the real world we are exposed to multiple stimuli at the same time.

Our result regarding the preference of happy speech over other types of emotional speech in infant brain at two-months of age should be explored further to understand the long-term implications on child socio-emotional development. In order to achieve this goal, long-term follow-up studies are needed to understand the development of emotional processing over the course of childhood.

We found that high maternal pregnancy-specific anxiety symptoms at gestation week 24 were associated with attenuated infant brain response to sad speech at two months of age. Given that ours is the first study to report this association, it is important for the future research to replicate these findings with other samples. Furthermore, it would be useful to examine if there is a cause-and-effect relationship between maternal pregnancy-related anxiety symptoms and blunted infant emotional responses to negative emotional stimuli. It would also be highly valuable to investigate maternal psychological distress at different time points of pregnancy and unraveling the effects of maternal personality traits, generalized anxiety during pregnancy, co-morbidity due to depression and paternal distress symptoms on the emotional processing in infant brain.

Our finding that affective touch is processed in the left IFG and left middle temporal gyrus in two-year-old children, for the first time, depicts the neuronal processing of social touch in two-year-olds. Future work on social touch in toddlers and older children is needed to understand the maturation of touch processing over the course of childhood. Further, long-term implications of affective touch on socio-emotional development of children need to be explored in close follow-up longitudinal studies. As these brain areas (left IFG and middle temporal gyrus) are important in socio-emotional processes, we hope that our study forms a groundwork for future studies inquiring whether attenuated responses to affective touch might be used as an early clinical biomarker for children with disrupted social-emotional development, e.g., ASD.

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